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(54) Title: 98 HUMAN SECRETED PROTEINS (57) Abstract The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.		

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98 Human Secreted Proteins

Field of the Invention

This invention relates to newly identified polynucleotides and the polypeptides encoded by these polynucleotides, uses of such polynucleotides and polypeptides, and
5 their production.

Background of the Invention

Unlike bacterium, which exist as a single compartment surrounded by a membrane, human cells and other eucaryotes are subdivided by membranes into many functionally distinct compartments. Each membrane-bounded compartment, or
10 organelle, contains different proteins essential for the function of the organelle. The cell uses "sorting signals," which are amino acid motifs located within the protein, to target proteins to particular cellular organelles.

One type of sorting signal, called a signal sequence, a signal peptide, or a leader sequence, directs a class of proteins to an organelle called the endoplasmic
15 reticulum (ER). The ER separates the membrane-bounded proteins from all other types of proteins. Once localized to the ER, both groups of proteins can be further directed to another organelle called the Golgi apparatus. Here, the Golgi distributes the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes, and the other organelles.

20 Proteins targeted to the ER by a signal sequence can be released into the extracellular space as a secreted protein. For example, vesicles containing secreted proteins can fuse with the cell membrane and release their contents into the extracellular space - a process called exocytosis. Exocytosis can occur constitutively or after receipt of a triggering signal. In the latter case, the proteins are stored in
25 secretory vesicles (or secretory granules) until exocytosis is triggered. Similarly, proteins residing on the cell membrane can also be secreted into the extracellular space by proteolytic cleavage of a "linker" holding the protein to the membrane.

Despite the great progress made in recent years, only a small number of genes encoding human secreted proteins have been identified. These secreted proteins
30 include the commercially valuable human insulin, interferon, Factor VIII, human growth hormone, tissue plasminogen activator, and erythropoietin. Thus, in light of

the pervasive role of secreted proteins in human physiology, a need exists for identifying and characterizing novel human secreted proteins and the genes that encode them. This knowledge will allow one to detect, to treat, and to prevent medical disorders by using secreted proteins or the genes that encode them.

5

Summary of the Invention

The present invention relates to novel polynucleotides and the encoded polypeptides. Moreover, the present invention relates to vectors, host cells, antibodies, and recombinant methods for producing the polypeptides and polynucleotides. Also provided are diagnostic methods for detecting disorders related to the polypeptides, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying binding partners of the polypeptides.

15

Detailed Description

Definitions

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide.

In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

In specific embodiments, the polynucleotides of the invention are less than 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, or 7.5 kb in length. In a further embodiment, polynucleotides of the invention comprise at least 15 contiguous nucleotides of the coding sequence, but do not comprise all or a portion of any intron.

5 In another embodiment, the nucleic acid comprising the coding sequence does not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene in the genome).

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X or the cDNA contained within the clone

10 deposited with the ATCC. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without the signal sequence, the secreted protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a

15 molecule having the translated amino acid sequence generated from the polynucleotide as broadly defined.

In the present invention, the full length sequence identified as SEQ ID NO:X was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID

20 NO:X was deposited with the American Type Culture Collection ("ATCC"). As shown in Table 1, each clone is identified by a cDNA Clone ID (Identifier) and the ATCC Deposit Number. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of

25 microorganisms for purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, the complement thereof, or the cDNA within the clone deposited with the ATCC. "Stringent hybridization conditions" refers to an

30 overnight incubation at 42° C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's

solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C.

Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions.

5 Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M

10 NaH_2PO_4 ; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 µg/ml salmon sperm blocking DNA; followed by washes at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress

15 background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

20

Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid

25 molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone).

The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of

30 single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA

that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA
5 backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

The polypeptide of the present invention can be composed of amino acids
10 joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more
15 detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of
20 modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a
25 heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation,
30 iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination.

(See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

"SEQ ID NO:X" refers to a polynucleotide sequence while "SEQ ID NO:Y" refers to a polypeptide sequence, both sequences identified by an integer specified in Table 1.

"A polypeptide having biological activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention.)

Polynucleotides and Polypeptides of the Invention

FEATURES OF PROTEIN ENCODED BY GENE NO: 1

The translation product of this gene is a human glycoprotein-associated amino acid transporter (See, e.g., Genbank Accession No. emb|CAA10198.1| (AJ130718); all references available through this accession are hereby incorporated by reference herein). Amino acid transport across cellular membranes is mediated by multiple transporters with overlapping specificities. The transport system L, which mediates Na⁺-independent exchange of large neutral amino acids, consists of a novel amino acid permease-related protein (LAT1 or AmAT-L-lc) which for surface expression and function requires formation of disulfide-linked heterodimers with the glycosylated heavy chain of the h4F2/CD98 surface antigen. h4F2hc also associates with other mammalian light chains, e.g. y+LAT1 from mouse and human which are

approximately 48% identical with LAT1 and thus belong to the same family of glycoprotein-associated amino acid transporters.

The novel heterodimers form exchangers which mediate the cellular efflux of cationic amino acids and the Na⁺-dependent uptake of large neutral amino acids.

- 5 These transport characteristics and kinetic and pharmacological fingerprints identify them as y⁺L-type transport systems. mRNA encoding y⁺LAT1 is detectable in most adult tissues and expressed at high levels in kidney cortex and intestine. This indicates that the y⁺LAT1-4F2hc heterodimer, besides participating in amino acid uptake/secretion in many cell types, is the basolateral amino acid exchanger involved
10 in transepithelial reabsorption of cationic amino acids; hence, its defect might be the cause of the human genetic disease lysinuric protein intolerance.

The gene encoding the disclosed cDNA is believed to reside on chromosome 14. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 14.

- 15 Preferred polypeptides comprise the following amino acid sequence:
LALYSALFSYSGWDTLN (SEQ ID NO: 237), VTEEIKNPERNLPL (SEQ ID NO: 238), IGISMPIVT (SEQ ID NO: 239), IYILTNVAYYTVL (SEQ ID NO: 240), SDA
VAVTFADQ (SEQ ID NO: 241), VALSCFGGLNASI (SEQ ID NO: 242), SRLFFV
GSREGHLPD (SEQ ID NO: 243), SFSYWFFVGLS (SEQ ID NO: 244), VGQLYLR
20 WKEP (SEQ ID NO: 245), RPRPLKLSVFFPIVFC (SEQ ID NO: 246), DTINSLIGI
(SEQ ID NO: 247), LLAAACICLLTFINCA YVKWGTLVQDIFTYAKVLALIAVI
VAGIVRLGQGASTHFENSFEGSSFAVGDIALLYSALFSYSGWDTLNYVTEEI
KNPERNLPLSIGISMPIVTIYILTNVAYYTVLDMRDILASDAVAVTFADQIFGIF
NWIPLSVALSCFGGLNASIVAASRLFFVGSREGHLPDAICMIHVERFTPVPSLL
25 FNGIMALIYLCVEDIFQLINYYSFSYWFFVGLSIVGQLYLRWKEPDRPRPLKLS
VFFPIVFCLCTIFLVAVPLYSDTINSLIGIAIALSGLPFYFLIIRVPEHKRPLYLRRI
VGSATRYLQVLCMSVAAEMDLEDGGEMPKQRDPKSN (SEQ ID NO: 249)
and/or ATALPPKIVGSATRYLQVLCMSVAAEMDLEDGGEMPKQRDPKSN
(SEQ ID NO: 248). Polynucleotides encoding these polypeptides are also provided.

- 30 Contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of THP-1 monocyte cells to calcium. Thus, it is likely that the product of this gene is involved in a signal

transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of both THP-1 monocytes, in addition to other cell-lines or tissue cell types. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating monocytes.

5 This gene is expressed primarily in endothelial cells and brain, and, to a lesser extent, in a wide variety of human tissues.

 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
10 not limited to, disorders of the neural or gastrointesinal systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the circulation system or central nervous system, expression of this gene at significantly higher or
15 lower levels is routinely detected in certain tissues or cell types (e.g., neural, gastrointestinal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not
20 having the disorder.

 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 124 as residues: Glu-102 to Asn-110, Arg-256 to Leu-266, Pro-316 to Trp-328, Pro-331 to Arg-336, Met-350 to Gly-358.

Polynucleotides encoding said polypeptides are also provided.

25 The tissue distribution in brain combined with its homology to a amino acid transporter and biological activity of increasing ion flux in monocytes indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the
30 "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease,

Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, 5 learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, 10 neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show 15 utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:11 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically 20 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1550 of SEQ ID NO:11, b is an integer of 15 to 1564, where both a and b correspond to the positions of nucleotide 25 residues shown in SEQ ID NO:11, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 2

The gene encoding the disclosed cDNA is believed to reside on the X chromosome. Accordingly, polynucleotides related to this invention are useful as a 30 marker in linkage analysis for the X chromosome.

Preferred polypeptides of the invention comprise the following amino acid sequence:

AARGSGVRDPLEEAVCPFSDLQLHAGRTTALFKAVRQGHLSLQRLLLSFVCL
CPAPRGGAYRGRQASLSCGGLHPVRASRLCLPKQAWAMAGAPPPVSLPPCS
LISDCCASNQRDSVG (SEQ ID NO: 250). Polynucleotides encoding these
polypeptides are also provided.

5 This gene is expressed primarily in cord blood cells, and, to a lesser extent, in
frontal lobe of the brain.

 Therefore, polynucleotides and polypeptides of the invention are useful as
reagents for differential identification of the tissue(s) or cell type(s) present in a
biological sample and for diagnosis of diseases and conditions which include, but are
10 not limited to, developmental, reproductive, hematopoietic or neural disorders.
Similarly, polypeptides and antibodies directed to these polypeptides are useful in
providing immunological probes for differential identification of the tissue(s) or cell
type(s). For a number of disorders of the above tissues or cells, particularly of the
immune and central nervous systems, expression of this gene at significantly higher or
15 lower levels is routinely detected in certain tissues or cell types (e.g., immune,
developmental, or cancerous and wounded tissues) or bodily fluids (e.g., lymph,
amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue
or cell sample taken from an individual having such a disorder, relative to the
standard gene expression level, i.e., the expression level in healthy tissue or bodily
20 fluid from an individual not having the disorder.

 Preferred polypeptides of the present invention comprise immunogenic
epitopes shown in SEQ ID NO: 125 as residues: His-56 to Gln-65, Leu-80 to Ile-85.
Polynucleotides encoding said polypeptides are also provided.

 The tissue distribution in cord blood cells indicates polynucleotides and
25 polypeptides corresponding to this gene are useful for the treatment and diagnosis of
hematopoietic related disorders such as anemia, pancytopenia, leukopenia,
thrombocytopenia or leukemia since stromal cells are important in the production of
cells of hematopoietic lineages. Representative uses are described in the "Immune
Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19,
30 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo
culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or
chemotherapy of neoplasia.

The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:12 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1743 of SEQ ID NO:12, b is an integer of 15 to 1757, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 3

This gene is expressed primarily in human T cell lymphomas.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, T cell lymphoma, immunodeficiencies, in addition to other immune system disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential
5 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample
10 taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 126 as residues: Met-1 to Phe-10. Polynucleotides
15 encoding said polypeptides are also provided.

The tissue distribution in human T cell lymphomas indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14,
20 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g., by boosting
25 immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory
30 bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity

disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:13 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1359 of SEQ ID NO:13, b is an integer of 15 to 1373, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 4

The protein product of this clone shares sequence homology with the C-terminus of a human N-acetylglucosamine-phosphate mutase (See, e.g., Genbank Accession No. gblAAC72409.11 (AF102265); all references available through this accession are hereby incorporated by reference herein.) Hofmann, et al. (Eur. J. Biochem. 221:741-747 (1994)) studied the N-acetylglucosamine-phosphate mutase of *Saccharomyces cerevisiae* and showed it to be essential for viability. A *S. cerevisiae* agm1 deletion mutant progressed through only approximately five cell cycles to form a 'string' of undivided cells with an abnormal cell morphology resembling

glucosamine auxotrophic mutants. Expression of the AGM1 gene on a multi-copy plasmid led to a significantly increased N-acetylglucosamine-phosphate mutase activity. Unlike over-expression of the *S. cerevisiae* AGM1 gene in a phosphoglucomutase (pgm1 delta/pgm2 delta) double deletion mutant which could
 5 restore phosphoglucomutase activity, over-expression of the PGM2 gene encoding the major isoenzyme of phosphoglucomutase did not increase N-acetylglucosamine-phosphate-mutase activity and did not restore growth of agm1 deletion mutant cells. These observations indicate that the different hexosephosphate mutases of *S.*
 10 *cerevisiae* have partially overlapping substrate specificities but, nevertheless, distinct physiological functions. The human N-acetylglucosamine-phosphate-mutase is expected to share at least some biological activities with the Agm1 protein.

Preferred polypeptide fragments of the invention comprise the following amino acid sequences: LSKAFLDSPNRL LAVEMNTDHLRLTVPNGIGALKLRXM
 EHYFSQGLSVQLFNDGSKGKLNHL CGAD FVKSHQKPPQGMEIKSNERCCSFD
 15 GDADRIVYYYHDADGHFHLIDGDKIATLISSFLKELLVEIGESLNIGVVQTAYA
 NGSSTRYLEEVMKVPVYCTKTGVKHLHHKAQEFDIGVYFEANGHG TALFST
 AVEMKIKQSAEQLEDKKRKA AKMLENIIDLFNQAAGDAISDMLVIEAILALK
 GLTVQQWDALYTDLPNRQLKVQVADRRVISTTXAERQAVTPPGLQEAINDL
 VKKYKLSRAFVRPSGTEDVVRVYAEADSQESADHLAHEVSLAVFQLAGGIGE
 20 RPQPGF (SEQ ID NO: 251), LSKAFLDSPNRL LAVEMNTDHLRLTV (SEQ ID
 NO: 252), PNGIGALKLRXMEHYFSQGLSVQLFNDG (SEQ ID NO: 253), SKGKL
 NHL CGAD FVKSHQKPPQGMEIKS (SEQ ID NO: 254), NERCCSFDGDADRIV
 YYYHDADGHFHLI (SEQ ID NO: 255), DGDKIATLISSFLKELLVEIGESLNIGV
 (SEQ ID NO: 256), VQTAYANGSSTRYLEEVMKVPVYCTKTG (SEQ ID NO:
 25 257), VKHLHHKAQEFDIGVYFEANGHG TALFS (SEQ ID NO: 258), TAVEMK
 IKQSAEQLEDKKRKA AKMLENI (SEQ ID NO: 259), IDLFNQAAGDAISDM
 LVIEAILALKGLT (SEQ ID NO: 260), VQQWDALYTDLPNRQLKVQVADRR
 VIST (SEQ ID NO: 261), TXAERQAVTPPGLQEAINDLVKKYKLSR (SEQ ID
 NO: 262), AFVRPSGTEDVVRVYAEADSQESA (SEQ ID NO: 263), and/or DH
 30 LAHEVSLAVFQLAGGIGERPQPGF (SEQ ID NO: 264). Polynucleotides encoding
 these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 6. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 6.

5 This gene is expressed primarily in fetal brain, and, to a lesser extent, in a wide variety of human tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental disorders, particularly of the central nervous system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central and peripheral nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 127 as residues: Asn-36 to Lys-42, Lys-53 to Gln-60, Ile-64 to Ala-77, Ala-128 to Tyr-135, Lys-184 to Ala-199, Leu-245 to Leu-250. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution of N-acetylglucosamine-phosphate mutase in fetal brain indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital

malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition,
5 elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity,
10 to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
15 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:14 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
20 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3726 of SEQ ID NO:14, b is an integer of 15 to 3740, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:14, and where b is greater than or equal to a + 14.

25 **FEATURES OF PROTEIN ENCODED BY GENE NO: 5**

This gene is expressed primarily in human stomach and stomach tumor cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
30 not limited to, disorders of the gastrointestinal system, particularly cancer or ulcers of stomach tissue. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the

tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., gastrointestinal, or cancerous and wounded tissues) or bodily fluids (e.g., bile, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in tumors of the stomach indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis, treatment and intervention of these tumors, in addition to other tumors where expression has been indicated. Additionally, the protein product of this gene may play a role in the normal function of the stomach and/or digestive system. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:15 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1182 of SEQ ID NO:15, b is an integer of 15 to 1196, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where b is greater than or equal to a + 14.

30 FEATURES OF PROTEIN ENCODED BY GENE NO: 6

Preferred polypeptides of the invention comprise the following amino acid sequences:

FEIALPRESNITVLIKLGTPTLLAKPCYIVISKRHITMLSIKSGERIVFTFSCQSPE
 NHFVIEIQKNIDCMMSGPCPFGEVQLQPSTSLPTLNRTFIWDVKAHKSIGLELQ
 FSIPRLRQIGPGESCPDGVTHSISGRIDATVVRIGTFCSNGTVSRIKM (SEQ ID
 NO: 266), and/or GTRAAPGLGAWGRRSPPSFSPRRPRPGVMAGLNCGVSIAL
 5 LGVLLLGAARLPRGAFAFEIALPRESNITVLIKLGTPTLLAKPCYIVISKRHITM
 LSIKSGERIVFTFSCQSPENHFVIEIQKNIDCMMSGPCPFGEVQLQPSTSLPTLN
 RTFIWDVKAHKSIGLELQFSIPRLRQIGPGESCPDGVTHSISGRIDATVVRIGTF
 CSNGTVSRIKMQEGVKMALHLPWFHPRNVSGFSIANRSSIKRLCIIESVFEGEGS
 ATLMSANYPEGFPDELMTWQFVVPAPHLRASVSFLNFNLSNCERKEERVEYY
 10 IPGSTTNPEVFKLEDKQPGNMAGNFNLSLQGCDDAQSPGILRLQFQVLVQH
 PQNESÑKIYVVDLSNERAMSLTIEPRPVKQSRKFVPGCFVCLESRTCSSNLT
 LTLTSGSKHKISFLCDDLTRLWMNVEKP (SEQ ID NO: 265). Polynucleotides encoding
 these polypeptides are also provided.

This gene is expressed primarily in placenta, and to a lesser extent in, prostate
 15 and ovary.

Therefore, polynucleotides and polypeptides of the invention are useful as
 reagents for differential identification of the tissue(s) or cell type(s) present in a
 biological sample and for diagnosis of diseases and conditions which include, but are
 not limited to, male and female infertility, and associated disorders of the
 20 reproductive system. Similarly, polypeptides and antibodies directed to these
 polypeptides are useful in providing immunological probes for differential
 identification of the tissue(s) or cell type(s). For a number of disorders of the above
 tissues or cells, particularly of the reproductive system, expression of this gene at
 significantly higher or lower levels is routinely detected in certain tissues or cell types
 25 (e.g., reproductive, or cancerous and wounded tissues) or bodily fluids (e.g., lymph,
 amniotic fluid, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or
 another tissue or cell sample taken from an individual having such a disorder, relative
 to the standard gene expression level, i.e., the expression level in healthy tissue or
 bodily fluid from an individual not having the disorder.

30 The tissue distribution of this gene in the prostate, placenta and ovary
 indicates that polynucleotides and polypeptides corresponding to this gene are useful
 for treatment, prevention, and/or diagnosis of male or female infertility, endocrine

disorders, fetal deficiencies, ovarian failure, amenorrhea, ovarian cancer, benign prostate hyperplasia and prostate cancer. Similarly, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. Expression within placental tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:16 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2195 of SEQ ID NO:16, b is an integer of 15 to 2209, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 7

The translation product of this gene shares homology with the human and rat HNK-1 sulfotransferase protein (See, e.g., Genbank Accession Nos. gblAAB88123.11 (AF022729) and gil2921306|gblAAC04707.11 (AF033827); all references available through these accessions are hereby incorporated herein by reference.) Ong E, et al. (J Biol Chem. 273(9):5190-5 (1998)) have characterized the human HNK-1 sulfotransferase, and show that it is involved in the synthesis of the HNK-1

carbohydrate epitope which is expressed on various adhesion molecules in the nervous system and on immune cells (e.g., natural killer cells) and is suggested to play a role in cell-cell and cell-substratum interactions. Based on the sequence similarity, the translation product of this gene is expected to share at least some biological activities with HNK-1 sulfotransferase proteins. Such activities are known in the art, some of which are described elsewhere herein, or in, for example, Bakker, et al., J Biol Chem. 272:29942-6 (1997), incorporated herein by reference. Based on sequence similarity between sulfotransferases, a consensus sequence for the active site was developed (Ong, et al., supra). The consensus pattern is as follows:

xxRPDzzzz, where x represents hydrophobic amino acid residues and z represents any amino acid residue. Therefore,

Preferred polypeptides of the invention comprise the following amino acid sequences: FVRDPFVRL (SEQ ID NO: 267), FLFVRDPFVRLIS (SEQ ID NO: 268), FLFVRDPFVRLISAF (SEQ ID NO: 269), and/or YLHTSFSRPHTGPPLPTPG PDRDRELTADSDVDEFLDKFLSAGVKQSDLPRKETEQPPAPGSMEENVRGY DWSPRDARRSPDQGRQQAERRSVLRGFCANSSLAFTKERAFDDIPNSELSHL IVDDRHGAIYCYVPKVACTNWKRVMIVLSGSLHHRGAPYRDPLRIPREHVH NASAHLTFNKFWRRYGKLSRHLMKVKLKKYTKFLFVRDPFVRLISAFRSK FELENEEFYRKFAVPMLRLYANHTSLPASAREAFRAGLKVSFANFIQYLLDPH TEKLAPFNEHWRQVYRLCHPCQIDYDFVGKLETLDAAQLLQLLQVDRQ LRFPPSYRNRTASSWEEDWFAKIPLAWRQQLYKLYEADFVLFGYPKPENLL RD (SEQ ID NO: 270). Polynucleotides encoding these polypeptides are also provided.

Further preferred are the sulfotransferase active site polypeptides listed above, and at least 5, 10, 15, 20, 25, 30, 50, or 75 additional contiguous amino acid residues of the sequence referenced in Table I for this gene. The additional contiguous amino acid residues is N-terminal or C-terminal to the sulfotransferase active site polypeptides. Alternatively, the additional contiguous amino acid residues is both N-terminal and C-terminal to the sulfotransferase active site polypeptides, wherein the total N- and C-terminal contiguous amino acid residues equal the specified number. The above preferred polypeptide domains are characteristic of a signature specific to sulfotransferase proteins. The nucleotides sequence of this gene was found to be

homologous to the human hypoxanthine guanine phosphoribosyl transferase 2 cDNA which is known to be involved in the purine salvage pathway resulting in the maintenance of homeostatic levels of uric acid (See Genbank Accession No. T30127).

The gene encoding the disclosed cDNA is believed to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

This gene is expressed to a very high level in HL-60 myelogenous leukemia cell lines, and to a lesser extent, in most cell types of the immune system.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, myelopoiesis, and metabolic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, metabolic, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 130 as residues: Ser-39 to Gly-46, Leu-49 to Ala-62, Lys-79 to Ala-93, Gly-95 to Asp-105, Ser-107 to Val-127, Gly-193 to Leu-200, Lys-218 to Ser-227, Lys-234 to Thr-239, Pro-366 to Asp-379, Pro-406 to Asp-414. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in HL-60 myelogenous leukemia cell lines and homology to HNK-1 sulfotransferase proteins indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, prevention and/or treatment of a variety of immune system disorders, including but not limited to, those involving the HNK-1 carbohydrate epitope, (e.g. HNK-1 as an auto-antigen

in peripheral demyelinating neuropathy). Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, expression of this gene product in tonsils indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g., by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the homology to a conserved purine metabolism protein may suggest that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, prevention, and/or treatment of various metabolic disorders such as Tay-Sach's Disease, phenylketonuria, galactosemia, porphyrias, Hurler's syndrome, and various urogenital disorders related to metabolic conditions, particularly Lesch-Nyhan syndrome. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:17 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1760 of SEQ ID NO:17, b is an integer of 15 to 1774, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 8

When tested against Jurkat T-cell lines, supernatants removed from cells containing this gene activated the gamma activating sequence (GAS) promoter element. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway, a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. Thus, it is likely that this gene activates T-cells through the Jak-STAT signal transduction pathway.

In a specific embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: KLVRLQVPVRNSRVDPRVRSKIGSRRWMLQLI
MQLGSVLLTRCPFWGCFSQLMLYAERAEARRKPDIPVPYLYFDMGAAVLCA
SFMSFGVKRRWFALGAALQLAISTYAAAYIGGYVHYGDWLKVRMYSRTVAII
GGFLVLASGAGELYRRKPRSRSLQSTGQVFLGIYLICVAYSLQHSKEDRLA
YLNHLPGGELMIQLFFVLYGILALAFLSGYVTLAAQILAVLLPPVMLLIDG
NVAYWHNTRRVEFWNQMKLLGESVGIFGTAVILATDG (SEQ ID NO: 271).

A preferred polypeptide fragment of the invention comprises the following amino acid sequence: MQLGSVLLTRCPFWGCFSQLMLYAERAEARRKPDIPVPYLYFDMGAAVLCASFMSFGVKRRWFALGAALQLAISTYAAAYIGGYVHYGD

WLKVRMYSRTVAIIGGFLVLASGAGELYRRKPRSRSLQSTGQVFLGIYLICVA
YSLQHSKEDRLAYLNHLPGGELMIQLFFVLYGILAPGLSVRLLRDPRCPDPGC
TAAPCHAAH (SEQ ID NO: 272). Polynucleotides encoding these polypeptides are
also provided.

5 The gene encoding the disclosed cDNA is believed to reside on chromosome
17. Accordingly, polynucleotides related to this invention are useful as a marker in
linkage analysis for chromosome 17.

 This gene is expressed primarily in endometrial tumors, and to a lesser extent,
in T-cells, pituitary and to a certain extent in most cell types.

10 Therefore, polynucleotides and polypeptides of the invention are useful as
reagents for differential identification of the tissue(s) or cell type(s) present in a
biological sample and for diagnosis of diseases and conditions which include, but are
not limited to, female reproductive, immune, or endocrine disorders. Similarly,
polypeptides and antibodies directed to these polypeptides are useful in providing
15 immunological probes for differential identification of the tissue(s) or cell type(s). For
a number of disorders of the above tissues or cells, particularly of the reproductive
and/or immune systems expression of this gene at significantly higher or lower levels
is routinely detected in certain tissues or cell types (e.g., immune, reproductive, or
cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, lymph, serum,
20 plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken
from an individual having such a disorder, relative to the standard gene expression
level, i.e., the expression level in healthy tissue or bodily fluid from an individual not
having the disorder.

 Preferred polypeptides of the present invention comprise immunogenic
25 epitopes shown in SEQ ID NO: 131 as residues: Ala-27 to Asp-34, Tyr-116 to Leu-
125. Polynucleotides encoding said polypeptides are also provided.

 The tissue distribution predominantly in the endometrium indicates that
polynucleotides and polypeptides corresponding to this gene are useful for the
detection, treatment, and/or prevention of a range of immune and/or reproductive
30 disorders including endometriosis, endometritis, and endometrioma. Similarly, the
tissue distribution in T-cells and the ability of supernatants expressing this gene to
stimulate the GAS promoter element in T-cells indicates polynucleotides and

polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g., by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the tissue distribution in pituitary indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers. Representative uses are described in the "Biological Activity", "Hyperproliferative Disorders", and "Binding Activity" sections below, in Example 11, 17, 18, 19, 20 and 27, and elsewhere herein. Briefly, the protein can be used for the detection, treatment, and/or prevention of the Addison's Disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g., diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-

hypopituitarism), thyroid (e.g., hyper-, hypothyroidism), parathyroid (e.g., hyper-, hypoparathyroidism), hypothalamus, and testes.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:18 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1660 of SEQ ID NO:18, b is an integer of 15 to 1674, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 9

Contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of the myeloid leukemia cell line AML-193 to calcium. Thus, it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of myeloid leukemia cells, in addition to other cell-lines or tissue cell types. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating myeloid leukemia cells.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: SNEILLSFPQNYIQLNGSLIHGLWNLASLFS NLCLFVLMPPFAFFLESEGFAGLKKGIRARILETLVMLLLLALLILGIVWVAS ALIDNDAASMESLYDLWEFYLPYLYSCISLMGCLLLLCTPVGLSRMFTVMG HLLVKPTILEDLDEQIYITLEEEALQRRNLGLSSSVVEYNIMELEQELENVKTL KTKLERRKKASAWERNLVYPAVMVLLLIETSSISVLLVACNILCLLVDETAM PKGTRGPGIGNASLSTFGFVGAALEIILIFYLMVSSVVGFYSLRFFGNFTPKKD DTTMTKIIGNCVSILVLSSALPMSRTLGITRFDLLGDFGRFNWLGNFYIVLS YNLLFAIVTTLCLVRKFTSAVREELFKALGLHKLHLPNTSRDSETAKPSVNGH

QKAL (SEQ ID NO: 273). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in fetal heart, and to a lesser extent, in colon and the adult pulmonary system.

5 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, heart, lung and digestive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological
10 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular, pulmonary and digestive systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., developmental, cardiovascular, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid,
15 serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic
20 epitopes shown in SEQ ID NO: 132 as residues: Glu-67 to Asn-74, Glu-88 to Asn-93, Lys-95 to Ala-107, Ala-147 to Arg-153, Phe-197 to Thr-205, Pro-292 to His-308. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in fetal heart, colon and pulmonary tissues and the biological activity in increasing the permeability of the plasma membrane of the
25 myeloid leukemia cell line AML-193 to calcium, likely indicating that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of myeloid leukemia cells, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment, prevention, and/or detection of a range of disorders including
30 a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease, vascular leak syndrome, aneurysm, stroke, embolism, myocardial infarction, myocarditis, ischemia, thrombosis, coronary artery disease,

arteriosclerosis, and/or atherosclerosis; pulmonary edema and embolism, bronchitis and/or cystic fibrosis; Crohn's Disease and/or colon cancer. Similarly, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:19 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2004 of SEQ ID NO:19, b is an integer of 15 to 2018, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 10

The protein product of this clone shares sequence homology with the human MaxiK channel beta 2 subunit (See, Genbank Accession No.

gb|AAD23380.1|AF099137_1 (AF099137); all references available through this

accession are hereby incorporated herein by reference), which is believed to be a modulatory subunit of the voltage and Ca²⁺ activated K⁺ (MaxiK) channel.

Additionally, this protein shares homology to the human calcium-activated potassium

channel beta subunit, which, when combined with its corresponding alpha subunit and modulating peptide, are believed to be useful in treating asthma, angina, hypertension, incontinence, migraine, irritable bowel syndrome (IBS). The subsequent heteromultimer that forms upon combining the alpha, beta, and modulator subunits are also thought to be useful in preventing premature labour, preventing and treating cerebral ischemia, inducing pain modulation and decreasing neurogenic inflammation in a patient (See GeneSeq Accession No. R85306).

Preferred polypeptides comprise the soluble domain which consists of the following amino acid sequence: RSYMQSVWTEESQCTLLNASITETFNCSFSCGP
DCWKLSQYPCLQVYVNLTSSEKLLLYHTEETIKINQKCSYIPKCGKNFEESM
SLNVVMENFRKYQHFCYSDEPNQKSVILTKLYSSNVLFHSLFWPTCMMA
GGVAIVAMVKLTQYLSLLCERIQRINR (SEQ ID NO: 274). Polynucleotides encoding these polypeptides are also provided. Based on the sequence similarity, the translation product of this gene is expected to share at least some biological activities with modulatory subunits of voltage and Ca²⁺ activated K⁺ channel proteins. Such activities are known in the art, some of which are described in Wallner, et al., PNAS 96:4137-4142 (1999), incorporated herein by reference.

This gene is expressed primarily in adrenal gland tumor, and to a lesser extent, in Hodgkin's lymphoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endocrine and immune disorders, particularly Hodgkin's Lymphoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and/or endocrine systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, endocrine, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression

level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 133 as residues: Trp-25 to Gln-30, Pro-50 to Gln-57,
5 Pro-93 to Glu-101, Arg-114 to Cys-121, Ser-123 to Gln-129, Ile-177 to Arg-182. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in adrenal gland tumor and its identification as the modulatory subunit of the voltage and Ca^{2+} activated K^{+} (MaxiK) channel indicates that polynucleotides and polypeptides corresponding to this gene are useful for the
10 detection, treatment, and/or prevention of various endocrine disorders and cancers, particularly Addison's Disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g., diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g., hyper-, hypothyroidism), parathyroid (e.g., hyper-, hypoparathyroidism), hypothalamus, and testes. Alternatively, expression in
15 proliferative immune tissues combined with its homology to a novel human K channel indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein.
20 Briefly, the expression of this gene product in Hodgkin's lymphoma indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g., by boosting immune
25 responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory
30 bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity

disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:20 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2084 of SEQ ID NO:20, b is an integer of 15 to 2098, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 11

The translation product of this gene shares homology with collagen and collagen like proteins (See, e.g., Genbank Accession Nos. gil29205351|gb|AAC39658.11 (AF018081) and gil2384942|gb|AAB69961.11 (AF022985); all references available through these accession numbers are hereby incorporated by reference herein). Additionally, it has been determined that this gene has homology to the human Kruppel related zinc finger protein (HTF10) which is known to be important as a transcription factor, particularly in development (See Genebank Accession No.L11672).

In a specific embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: AFAHLQLGPMWKLWRAEEGAAALGGALFLLL
5 FALGVRQLLKQRRPMGFPPGPPGLPFIGNIYSLAASSELPHVYMRKQSQVYG
EVQPRRAPGREGRQAGPGWPGPSWLDLWPPLGRLVGTSPCAGCPLRDTRFPG
LEGRS PRRRAPLQGEPRPCR (SEQ ID NO: 275). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in human erythroleukemia cell line (HEL),
10 serum induced smooth muscle, and to a lesser extent in human 8 week whole embryo.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, leukemia, musculoskeletal, or developmental disorders. Similarly,
15 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic system and muscular system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune,
20 musculoskeletal, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 134 as residues: Leu-30 to Gly-38, Arg-67 to Val-72, Val-76 to Ala-89, Pro-118 to Arg-123, Gly-129 to Ala-136, Leu-138 to Arg-146. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in human erythroleukemia cell line (HEL), and serum
30 induced smooth muscle, and the shared homology with collagen and collagen like proteins indicates that polynucleotides and polypeptides corresponding to this gene are useful for disorders of hematopoietic or muscular systems, such as leukemia and

muscular dystrophy. Additionally, the shared homology with collagen proteins would suggest that this protein may also be important in the diagnosis or treatment of various autoimmune disorders (i.e., rheumatoid arthritis, lupus, scleroderma, dermatomyositis, etc.), dwarfism, spinal deformation, joint abnormalities, and
5 chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid, etc.).

The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents
10 that modulate their interactions and as nutritional supplements. It may also have a very wide range of biological activities although no evidence for any is provided in the specification. Typical of these are cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines;
immunostimulating/immunosuppressant activities (e.g., for treating human
15 immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of haematopoiesis (e.g., for treating anaemia or as adjunct to chemotherapy); stimulation of growth of bone, cartilage, tendons, ligaments and/or nerves (e.g., for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g., for treating
20 infections, tumours); haemostatic or thrombolytic activity (e.g., for treating haemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g., for treating septic shock, Crohn's Disease); as antimicrobials; for treating psoriasis or other hyperproliferative disease; for regulation of metabolism, behaviour, and many others. Also contemplated is the use of the corresponding nucleic acid in gene therapy
25 procedures. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:21 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
5 formula of a-b, where a is any integer between 1 to 1732 of SEQ ID NO:21, b is an integer of 15 to 1746, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 12

10 A preferred polypeptide fragment of the invention comprises the following amino acid sequence: MRVRIGLTLLCAVLLSLASASSDEEGSQD
ESLGFQDYFDIR (SEQ ID NO: 276). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome
15 8. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 8.

This gene is expressed primarily in dendritic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a
20 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at
25 significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an
30 individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 135 as residues: Ser-22 to Ser-41, Glu-43 to Thr-50,

Ser-63 to Leu-68, Ser-71 to Gly-84, Ser-96 to Gly-114. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in dendritic cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, prevention,
5 and/or treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including
10 blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g., by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for
15 immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity
20 disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have
25 commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

The secreted protein can be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents
30 that modulate their interactions and as nutritional supplements. It may also have a very wide range of biological activities although no evidence for any is provided in the specification. Typical of these are cytokine, cell proliferation/differentiation

modulating activity or induction of other cytokines;
immunostimulating/immunosuppressant activities (e.g., for treating human
immunodeficiency virus infection, cancer, autoimmune diseases and allergy);
regulation of haematopoiesis (e.g., for treating anaemia or as adjunct to
5 chemotherapy); stimulation of growth of bone, cartilage, tendons, ligaments and/or
nerves (e.g., for treating wounds, stimulation of follicle stimulating hormone (for
control of fertility); chemotactic and chemokinetic activities (e.g., for treating
infections, tumours); haemostatic or thrombolytic activity (e.g., for treating
haemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g., for treating
10 septic shock, Crohn's Disease); as antimicrobials; for treating psoriasis or other
hyperproliferative disease; for regulation of metabolism, behaviour, and many others.
Also contemplated is the use of the corresponding nucleic acid in gene therapy
procedures. Furthermore, the protein may also be used to determine biological
activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to
15 identify agents that modulate their interactions, in addition to its use as a nutritional
supplement. Protein, as well as, antibodies directed against the protein may show
utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
available and accessible through sequence databases. Some of these sequences are
20 related to SEQ ID NO:22 and may have been publicly available prior to conception of
the present invention. Preferably, such related polynucleotides are specifically
excluded from the scope of the present invention. To list every related sequence is
cumbersome. Accordingly, preferably excluded from the present invention are one or
more polynucleotides comprising a nucleotide sequence described by the general
25 formula of a-b, where a is any integer between 1 to 2862 of SEQ ID NO:22, b is an
integer of 15 to 2876, where both a and b correspond to the positions of nucleotide
residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 13

30 A preferred polypeptide variant of the invention comprises the following
amino acid sequence: MARGSLRRLRLVLGLWLALLRSVAGEQAPGTAPC
SRGSSWSADLDKCMDCSTSCPLPA ALAHPWGRSEPDLRAGAAFWLFGLE

TMPQE REVHHPHRGDRRRGLPSCGADPVTMCPLPAGARPLIIHSSILEPVSAS
QTRREPSSSNHK GGGGR (SEQ ID NO: 277). Polynucleotides encoding these
polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome
5 16. Accordingly, polynucleotides related to this invention are useful as a marker in
linkage analysis for chromosome 16.

This gene is expressed primarily in tumor growth factor or lipopolysaccharide
treated bone marrow stroma, epithelioid sarcoma, umbilical vein endothelial cells, and
to a lesser extent, in other tissues.

10 Therefore, polynucleotides and polypeptides of the invention are useful as
reagents for differential identification of the tissue(s) or cell type(s) present in a
biological sample and for diagnosis of diseases and conditions which include, but are
not limited to, hematopoiesis or immune disorders. Similarly, polypeptides and
antibodies directed to these polypeptides are useful in providing immunological
15 probes for differential identification of the tissue(s) or cell type(s). For a number of
disorders of the above tissues or cells, particularly of the hematopoietic,
integumentary, or immune systems expression of this gene at significantly higher or
lower levels is routinely detected in certain tissues or cell types (e.g., hematopoietic,
immune, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum,
20 plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken
from an individual having such a disorder, relative to the standard gene expression
level, i.e., the expression level in healthy tissue or bodily fluid from an individual not
having the disorder.

Preferred polypeptides of the present invention comprise immunogenic
25 epitopes shown in SEQ ID NO: 136 as residues: Pro-35 to Trp-42, Pro-65 to Asp-72,
Thr-86 to Phe-93, Ile-97 to Glu-103. Polynucleotides encoding said polypeptides are
also provided.

The tissue distribution in tumor growth factor or lipopolysaccharide treated
bone marrow stroma, epithelioid sarcoma, and umbilical vein endothelial cells
30 indicates that polynucleotides and polypeptides corresponding to this gene are useful
for the diagnosis, prevention, and/or treatment of a variety of immune system
disorders. Representative uses are described in the "Immune Activity" and "infectious

disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g., by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

The secreted protein can be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions and as nutritional supplements. It may also have a very wide range of biological activities although no evidence for any is provided in the specification. Typical of these are cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g., for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of haematopoiesis (e.g., for treating anaemia or as adjunct to chemotherapy); stimulation of growth of bone, cartilage, tendons, ligaments and/or nerves (e.g., for treating wounds, stimulation of follicle stimulating hormone (for

control of fertility); chemotactic and chemokinetic activities (e.g., for treating infections, tumours); haemostatic or thrombolytic activity (e.g., for treating haemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g., for treating septic shock, Crohn's Disease); as antimicrobials; for treating psoriasis or other
5 hyperproliferative disease; for regulation of metabolism, behaviour, and many others. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
10 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:23 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
15 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1038 of SEQ ID NO:23, b is an integer of 15 to 1052, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.

20 FEATURES OF PROTEIN ENCODED BY GENE NO: 14

The translation product of this gene shares sequence homology with chromaffin granule amine transporter protein which is thought to be important in vesicle membrane amine transport, particularly in the neural and endocrine tissue, and the human vesicular monoamine transporter hVMAT1 which is involved in the
25 regulation of amine storage in cardiovascular, endocrine, and central nervous system function (See, Genbank Accession Nos. gil1314290 and gblAAC50472.11; all references available through these accession numbers are hereby incorporated by reference herein). Based on these sequence similarities, The translation product of this gene is expected to share at least some biological activities with amine transporter
30 proteins. Such activities are known in the art, some of which are described in Erickson, et al., PNAS 93:5166-5171 (1996), and/or Liu, et al., Cell 70:539-551 (1992), which are both incorporated herein by reference.

In a specific embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: GTSFLDPTLSLFLVLEKFNLPAAGYVGLVFLGMAL
5 SYAISSPLFGLLSDKRPLRKWLLVFGNLITAGCYMLLGPVPILHIKSQLWLL
VLILVVSGLSAGMSIIPTFPEILSCAHENGFEGLSTLGLVSGLFSAWWSIGAF
MGPTLGGFLYEKIGFEWAAAIQGLWALISGLAMGLFYLLLEYSRRKRKSKSQNIL
STEEERTTLLPNET (SEQ ID NO: 278). Polynucleotides encoding these
polypeptides are also provided.

- 10 The gene encoding the disclosed cDNA is believed to reside on chromosome 6. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 6.

This gene is expressed primarily in colon cancer, osteoclastoma, and T-cell lymphoma, and to a lesser extent in many tumor or proliferative tissues such as
15 endometrial tumor, chondrosarcoma, induced umbilical vein endothelial cells.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases resulting from disorders in small molecule transport (i.e.,
20 signalling molecules) in afflicted tissues and organs, particularly of the endocrine and central nervous systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the musculoskeletal, immune, and/or digestive systems
25 and cancer expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, endocrine, or cancerous and wounded tissues) or bodily fluids (e.g., bile, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression
30 level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 137 as residues: Ser-114 to Asn-123, Thr-127 to Thr-132. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in colon cancer, osteoclastoma, and T-cell lymphoma
5 and homology to amine transporter family members indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of disorders or diseases resulted from small molecule transport in afflicted tissues and organs, particularly that of colon, osteoclast or T-cells. The expression in cancer tissues, and shared homology with transporter proteins may also indicate its role in
10 anti-cancer drug resistance. Additionally, the protein can be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands, to identify agents that modulate their interactions and as nutritional supplements. It may also have a very wide range of biological activities although no evidence for any is provided in the specification. Typical of these are cytokine, cell
15 proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of haematopoiesis (e.g. for treating anaemia or as adjunct to chemotherapy); stimulation of growth of bone, cartilage, tendons, ligaments and/or
20 nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumours); haemostatic or thrombolytic activity (e.g. for treating haemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's Disease); as antimicrobials; for treating psoriasis or other
25 hyperproliferative disease; or for identifying inhibitors or promoters of the transport of toxic molecules to vesicles, for regulation of metabolism, behaviour, and many others. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.
30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:24 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
5 formula of a-b, where a is any integer between 1 to 1527 of SEQ ID NO:24, b is an integer of 15 to 1541, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 15

10 The translation product of this gene shares sequence homology with the human prolyl 4-hydroxylase alpha (II) subunit which is important in catalyzing the formation of 4-hydroxyproline in collagens which is essential for the folding of newly synthesised collagen polypeptide chains into triple-helical molecules (See Genbank Accession No. gb|AAB71339.1|; all references available through this accession are
15 hereby incorporated herein by reference). Based on the sequence similarity, the translation product of this gene is expected to share at least some biological activities with Prolyl 4-hydroxylase proteins. Such activities are known in the art, some of which are described in Annunen, et al., J. Biol. Chem. 272:17342-17348 (1997) which is incorporated herein by reference.

20 When tested against U937 myeloid and Jurkat T-cell cell lines, supernatants removed from cells containing this gene activated the gamma activating sequence (GAS), a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the
25 Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. Thus, it is likely that this gene activates myeloid cells and T-cells through the Jak-STAT signal transduction pathway.

In a specific embodiment, polypeptides comprising the amino acid sequence
30 of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

GTREARLRDLTRFYDKVLSLHEDSTTPVANPLLAFTLIKRLQSDWRNVVHSL
 EASENIRALKDGYEKVEQDLPAFEDLEGAARALMRLQDVYMLNVKGLAR
 GVFQRTGSAITDLYSPKRLFSLTGDDCFQVGKVA YDMGDYYHAIPWLEEA
 VSLFRGSYGEWKTEDEASLEDALDHLAFAYFRAGNVSCALSLSREFLLYSPD
 5 NKRMARNVLK YERLLAESPNHVVAEAVIQRPNIPHLQTRDTYEGLCQTL
 GSQPTLYQIPSLYCSYETNSNAYLLLQPIRKEVIHLEPYIALYHDFVSDSEAQ
 KIRELAEPWLQRSVVASGEKQLQVEYRISKSAWLKDTVDLKLVTLNHRIAA
 LTGLDVRPPYAEYLQVVNYGIGGGHYEPHFDHATSPSSPLYRMKSGNRVATFM
 IYLSSVEAGGATAFIYANLSVPVVRNAALFWWNLHRSGEGDSDTLHAGCP
 10 VLVGDKWVANKWIHEYGQEFRRPCSSSPED (SEQ ID NO: 282). Additional,

Preferred polypeptides comprise the following amino acid sequence: GTREA
 RLRDLTRFYDKVLSLHEDSTTPVANPLLAFTLIKRLQSDWRNVVHSL EASENI
 RALKDGYEKVEQ DLPAFEDLEGAARAL (SEQ ID NO: 279), ALMRLQD (SEQ
 ID NO: 280), and/or VEAGGAT (SEQ ID NO: 281). Polynucleotides

15 encoding these polypeptides are also provided.

This gene is expressed primarily in lymph node breast cancer, colon
 carcinoma, and to a lesser extent in osteoblasts and adipocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as
 reagents for differential identification of the tissue(s) or cell type(s) present in a
 20 biological sample and for diagnosis of diseases and conditions which include, but are
 not limited to, disorders of connective and immune tissues, particularly autoimmune
 disorders. Similarly, polypeptides and antibodies directed to these polypeptides are
 useful in providing immunological probes for differential identification of the
 tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,
 25 particularly of the connective tissues in breast, colon, bone, and fat, expression of this
 gene at significantly higher or lower levels is routinely detected in certain tissues or
 cell types (e.g., immune, connective, or cancerous and wounded tissues) or bodily
 fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another
 tissue or cell sample taken from an individual having such a disorder, relative to the
 30 standard gene expression level, i.e., the expression level in healthy tissue or bodily
 fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 138 as residues: Ser-74 to Ala-84, Gln-156 to Tyr-161, Tyr-184 to Asn-189, Ser-218 to Ile-223, Pro-299 to Ser-308, His-359 to Thr-368, Tyr-390 to Asp-404. Polynucleotides encoding said polypeptides are also provided.

5 The tissue distribution in lymph node breast cancer and colon carcinoma and homology to prolyl 4-hydroxylase alpha (II) subunit indicates that polynucleotides and polypeptides corresponding to this gene are useful for intervention of connective tissue disorders and diseases (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), as well as, in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias ie. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid. Alternatively, the tissue distribution within various tissue carcinomas and tumor tissues, and biological activity reflected by the binding and activation of the GAS promoter element indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders.

15 Expression in cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

25 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:25 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2065 of SEQ ID NO:25, b is an

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integer of 15 to 2079, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 16

5 In an additional embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: IQPSHAALLHCRSTFRKTECLDPW
WVRRQLLG MAGIGGLQKMKAPHTGVLHLGSVWVFLGPFLG VGYTLTFNPL
10 SGCMSTVRWLNSNITANRTLRSVCHVTPLHRSLSPHDGEYLRQMLLNSSSR
AGEAGSWG Y (SEQ ID NO: 283). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 20. Accordingly, polynucleotides related to this invention are useful as a marker in
15 linkage analysis for chromosome 20.

This gene is expressed primarily in fetal liver, and, to a lesser extent, in a variety of fetal and other tissues and cell types.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a
20 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, liver disorders and cancers (e.g., hepatoblastoma, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential
25 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., hepatic, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an
30 individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 139 as residues: Ser-67 to Tyr-75. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in fetal liver indicates that polynucleotides and polypeptides corresponding to this gene are useful for detection and treatment of liver disorders and cancers (e.g., hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:26 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1933 of SEQ ID NO:26, b is an integer of 15 to 1947, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 17

The translation product of this gene shares sequence homology with human laminin B1 which is thought to be an important structural extracellular matrix component involved in cell migration and signalling, particularly in stimulating epithelial cell growth and differentiation (See, Genbank Accession No gill86837).

Preferred polypeptides of the invention comprise the following amino acid sequences: CSSPPGRLPWCWTAPRTLKGKHSGLISTLRLTAPLHLAWKMMLS RKALFVLLNTPVLFHALEGRLFSKLCHHHTIQRTLTVPKFRSS (SEQ ID NO: 284), RSPTS RVQLLKRQSCPCQRNDLNEEPQHFTHYAIYDFIVKGSCFCNG
 5 HADQCIPVHGFRPVKAPGTFHMHGKCM (SEQ ID NO: 285), and/or HNTAG SHCQHCAPLYNDRPWEAADGKTGAPNECRTCKCNGHADTCHFDVNVWEAS GNRSGGVCDQCQHNTEGQYCQRCKPGFYRDLRRPFSAPDACKPCSCHPV GSAVLPANSVTFCDPSTNGDCPCKPGVAGRRCDRCMVGYWGFGDYGCRP CDCAGSCDPITGDCISSHTDIDWYHEVPDFRPVHNKSEPAWEWEDAQGFSA
 10 LHSGKCECKEQTLGNAKAFCGMKYSYVLKIKILSAHDKGTHVEVNVKIK KVLKSTKLKIFRGKANIISRIMDGQ RMHLSNPQSWFGIPCSRT (SEQ ID NO: 286). Polynucleotides encoding these polypeptides are also provided.

Included in this invention as preferred domains are Laminin-type EGF-like (LE) domain signatures, which were identified using the ProSite analysis tool (Swiss
 15 Institute of Bioinformatics). Laminins are the major noncollagenous components of basement membranes that mediate cell adhesion, growth migration, and differentiation. They are composed of distinct but related alpha, beta and gamma chains. The three chains form a cross-shaped molecule that consist of a long arm and three short globular arms. The long arm consists of a coiled coil structure contributed
 20 by all three chains and cross-linked by interchain disulfide bonds. Beside different types of globular domains each subunit contains, in its first half, consecutive repeats of about 60 amino acids in length that include eight conserved cysteines. The tertiary structure of this domain is remotely similar in its N-terminal to that of the EGF-like module. It is known as a 'LE' or 'laminin-type EGF-like' domain. The number of
 25 copies of the LE domain in the different forms of laminins is highly variable; from 3 up to 22 copies have been found. A schematic representation of the topology of the four disulfide bonds in the LE domain is shown below.

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      +-----+
    +-|-----+   |   +-----+ +-----+
5   | |         |   |   |         |   |
    xxCxXXXXXXXXXXCXXXXXXXXCxxCxxxxGxxCxxCxxgaagXXXXXXXXXXCxx
                                *****
    sssssssssssssssssssssssssssssssssssssssssssss

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'C': conserved cysteine involved in a disulfide bond

'a': conserved aromatic residue

'G': conserved glycine (lower case = less conserved)

15 's': region similar to the EGF-like domain

'*': position of the pattern

In mouse laminin gamma-1 chain, the seventh LE domain has been shown to be the only one that binds with a high affinity to nidogen. The binding-sites are
 20 located on the surface within the loops C1-C3 and C5-C6. Long consecutive arrays of LE domains in laminins form rod-like elements of limited flexibility, which determine the spacing in the formation of laminin networks of basement membranes. We derived a signature pattern for the LE domain which covers the C-terminal half of the repeat starting with the fourth conserved cysteine. The consensus pattern is as
 25 follows: C-x(1,2)-C-x(5)-G-x(2)-C-x(2)-C-x(3,4)-[FYW]-x(3,15)-C [All C's are involved in disulfide bonds]

Preferred polypeptides of the invention comprise the following amino acid sequence: CDDCQHNTGQYCQRCKPGFYRDLRRPFSAPDACKPC (SEQ ID NO: 287) and/or CPCKPGVAGRRCDRCMVGYWGFGDYGCRPCDCAGSC (SEQ
 30 ID NO: 288). Polynucleotides encoding these polypeptides are also provided.

Further preferred are polypeptides comprising the laminin-type EGF-like domains listed above, and at least 5, 10, 15, 20, 25, 30, 50, or 75 additional contiguous amino acid residues of the sequence encoded by this gene. The additional contiguous amino acid residues is N-terminal or C-terminal to the laminin-type EGF-

like domain. Alternatively, the additional contiguous amino acid residues is both N-terminal and C-terminal to the laminin-type EGF-like domain, wherein the total N- and C-terminal contiguous amino acid residues equal the specified number. The above preferred polypeptide domain is characteristic of a signature specific to

5 Laminin proteins. Based on the sequence similarity, the translation product of this gene is expected to share at least some biological activities with Laminin proteins. Such activities are known in the art, some of which are described elsewhere herein.

This gene is expressed primarily in osteoblastic tissues and cell types, including osteoblasts, osteoblastomas and osteoclastomas. Expression is also

10 abundant in vascular-pulmonary tissues such as lung, micro-vasculature, pulmonary, endothelial and smooth muscle cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

15 not limited to, cancer and malignancies (particularly of osteoblastic tissues and rhabdomyosarcoma), as well as cardiovascular and respiratory or pulmonary disorders such as athsma, pulmonary edema, pneumonia, atherosclerosis, restenosis, stoke, thrombosis hypertension, inflammation and wound healing. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological

20 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardio-respiratory system, and skeletal system expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., skeletal, osteoblast, cardio-respiratory, vascular, or cancerous and wounded tissues) or bodily fluids (e.g., lymph,

25 pulmonary surfactant, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic

30 epitopes shown in SEQ ID NO: 140 as residues: Ser-28 to Cys-34, Thr-51 to Thr-58, Tyr-64 to Asn-81, Asp-111 to Lys-116, Asp-145 to Phe-160, Pro-203 to Glu-217. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in osteoblastic tissues and cell types and homology to laminin indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment, prevention and diagnosis of cardiovascular and respiratory or pulmonary disorders such as asthma, pulmonary edema, pneumonia, atherosclerosis, restenosis, stroke, angina, thrombosis hypertension, inflammation and wound healing. As a homolog of laminin, this gene product quite possibly has a role in cell adhesion, migration, proliferation, angiogenesis, chondrogenesis, wound healing and oncogenesis. An EST (Int J Cancer 1996 May 16;66(4):571-577) with an identical sequence to part of this contig was shown to be differentially expressed in human primary myoblasts and embryonal rhabdomyosarcoma and therefore might have an important role in the determination or maintenance of the normal phenotype, and thus its loss is possibly involved in the progression of malignancies, particularly of skeletal muscle. Similarly, the homology to a laminin would suggest a role in the detection and treatment of disorders and conditions afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation) in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:27 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 3365 of SEQ ID NO:27, b is an integer of 15 to 3379, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 18

The gene encoding the disclosed cDNA is believed to reside on chromosome 10. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 10.

10 In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: NISSQYCILKSLEMMISGLKLLVLFLKFAPENY CLSTETLQMPNRLRLSKATCYLMKCLLPSEYFE (SEQ ID NO: 289).

Polynucleotides encoding these polypeptides are also provided.

15 This gene is expressed primarily in placenta, brain, and to a lesser extent, in a variety of other tissues and cell types.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive, behavioral, or nervous system disorders, such as: depression, schizophrenia, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, dementia, paranoia, addictive behavior, epilepsy, transmissible spongiform encephalopathy (TSE), Creutzfeldt-Jakob disease (CJD). Other diseases and conditions related to expression in the placenta might include developmental anomalies and fetal deficiencies, ovarian and endometrial cancers, reproductive disfunction and pre-natal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous and reproductive systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, reproductive, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial

fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic
5 epitopes shown in SEQ ID NO: 141 as residues: Ala-16 to Leu-22. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions.
10 Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia,
15 trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, expression in placenta would suggest a
20 possible role in the treatment and diagnosis of developmental anomalies and fetal deficiencies, ovarian and endometrial cancers, reproductive dysfunction and pre-natal disorders.

Similarly, expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the
25 regulation of cellular division. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or
30 receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may

show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:28 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1992 of SEQ ID NO:28, b is an integer of 15 to 2006, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 19

The translation product of this gene shares sequence homology with the murine transforming protein (See, e.g., Genbank Accession No. gi53529|embl|CAA36859.1; all references available through this accession are hereby incorporated by reference herein).

In a specific embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: PIEGTPAGTGPEFPGRPTRPQRMRSLLISSHPCQHLLLLLLLLFLILAILVDVKWYLVLFICISLMTSDVEHLFMCLLAIRISSWRNVY (SEQ ID NO: 290). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in activated and basal T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunodeficiency, tumor necrosis, infection, lymphomas, auto-immunities, cancer, metastasis, wound healing, inflammation, anemias (leukemia) and other hematopoietic disorders. Similarly, polypeptides and antibodies directed to these

polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 The tissue distribution in activated T-cells and the homology to a murine transforming protein indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere
15 herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g., by boosting immune responses).

20 Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities,
25 such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, scleroderma and tissues. Moreover, the protein may represent a secreted
30 factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of

various blood lineages, and in the differentiation and/or proliferation of various cell types.

The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents
5 that modulate their interactions and as nutritional supplements. It may also have a very wide range of biological activities although no evidence for any is provided in the specification. Typical of these are cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human
10 immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of haematopoiesis (e.g. for treating anaemia or as adjunct to chemotherapy); stimulation of growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating
15 infections, tumours); haemostatic or thrombolytic activity (e.g. for treating haemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's Disease); as antimicrobials; for treating psoriasis or other hyperproliferative disease; for regulation of metabolism, behaviour, and many others. Also contemplated is the use of the corresponding nucleic acid in gene therapy
20 procedures. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

25 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:29 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
30 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3056 of SEQ ID NO:29, b is an

integer of 15 to 3070, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 20

5 The translation product of this gene was shown to have homology to the Mus musculus ALG-2 protein, which is known to code for a Ca(2+)-binding protein required for T cell receptor-, Fas-, and glucocorticoid-induced cell death. ALG-2 mediate Ca(2+)-regulated signals along the death pathway and may play a role in the onset of Alzheimer's Disease (See e.g., Genbank Accession No.gil1213520; all
10 references available through this accession are hereby incorporated by reference herein).

 Preferred polypeptides comprise the following amino acid sequence: NWVPT CLCPSAPCSFHLLSRFKCLFSPQRLTDIFRRYDTDQDGWIQVSYEQYLSMVFS
15 IV (SEQ ID NO: 291), and/or QRLTDIFRRYDTDQDGWIQVSYEQYLSMVFSIV (SEQ ID NO: 292). Polynucleotides encoding these polypeptides are also provided.

 When tested against K562 cell lines, supernatants removed from cells containing this gene activated the ISRE (interferon-sensitive responsive element). Thus, it is likely that this gene activates immune or leukemia cells through the Jaks-STAT signal transduction pathway. ISRE is a promoter element found upstream in
20 many genes which are involved in the Jaks-STAT pathway. The Jaks-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

25 A preferred polypeptide fragment of the invention comprises the following amino acid sequence: MFYKLTLLCELSVAGVTQAASQRPLQRLPRHICSQR XPPGRCLLKAXLQTTWXXPKPI PRLSPPLXSDPKR (SEQ ID NO: 293). Polynucleotides encoding these polypeptides are also provided.

 The gene encoding the disclosed cDNA is believed to reside on chromosome
30 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

This gene is expressed primarily in placenta, and to a lesser extent, in a variety of other tissues and cell types.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental anomalies, fetal deficiencies ovarian and endometrial cancers, reproductive dysfunction and pre-natal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, developmental, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 143 as residues: Arg-24 to Arg-31, Ile-33 to Gly-41. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in placenta indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment, prevention and/or diagnosis of developmental anomalies, fetal deficiencies, ovarian and endometrial cancers, reproductive dysfunction and pre-natal disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells combined with the observed ISRE activity, and homology to the apoptosis linked, ALG-2 indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:30 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2213 of SEQ ID NO:30, b is an integer of 15 to 2227, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 21

The translation product of this gene was shown to have homology to the human histo-blood group A transferase (See, e.g., Genbank Accession No. gblAAD26573.1|AF134413_1 (AF134413); all references available through this
 5 accession are hereby incorporated by reference herein) which is known to represent one of the major allogeneic antigens in both erythrocytes and tissues of humans. Its been proposed that the A phenotype is associated with the glycosyltransferas that converts the H substance associated with the O phenotype to A through the addition of alpha1-3-N-acetyl galactosamine or alpha1-3-galactosyl residues to the H antigen
 10 Fuc-alpha1-2Gal- beta1-R. Therefore, the primary product of the histo-blood group A is its respective glycosyltransferase. Preferred polypeptides of the invention comprise the following amino acid sequence: TSSPVFSFCSMAVREPDHLQ
 RVSLPRYNVSASLQWLPCHRIVLQPWHMCAMWELGQVLFHPVAPREGAAPS
 PVSTLTWPSSCSHSESTMELELQF (SEQ ID NO: 294), LPCHRIV (SEQ ID NO:
 15 296), SLQWLPCHRIVLQPW (SEQ ID NO: 297), and/or MAVREPDHLQRVSLPR (SEQ ID NO: 295). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in 12-week-old human embryo.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a
 20 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental anomalies, fetal deficiencies, pre-natal disorders, hematopoietic disorders, or cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above
 25 tissues or cells, particularly of the developing fetus, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., hematopoietic, lymph, developing, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder,
 30 relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in 12 week old embryo indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of developmental anomalies, fetal deficiencies, pre-natal disorders and cancer. Similarly, expression within embryonic tissue and other cellular sources marked by

5 proliferating cells indicates that this protein may play a role in the regulation of cellular division. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Alternatively, the tissue distribution and homology to human blood group A

10 and B glycosyltransferase enzymes indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "infectious

15 disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

The gene product may also be involved in lymphopoiesis, therefore, it can be

20 used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to

25 isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly

30 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:31 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1274 of SEQ ID NO:31, b is an integer of 15 to 1288, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 22

The translation product of this gene shares sequence homology with CD97 (EMR1), which is thought to be important in both adhesion and signaling processes early after leukocyte activation (See, e.g., Genbank Accession No. gil784994; all references available through this accession are hereby incorporated by reference herein). EMR1 belongs to a novel family of G-protein receptors that has recently been recognized on the basis of homologous primary amino acid sequences, comprises receptors to hormones of the secretin/vasoactive intestinal peptide/glucagon family, parathyroid hormone and parathyroid hormone-related peptides, growth hormone-releasing factor, corticotropin-releasing factor, and calcitonin. Proteins with seven transmembrane segments (7TM) define a superfamily of receptors (7TMreceptors) sharing the same topology: an extracellular N-terminus, three extramembranous loops on either side of the plasma membrane, and a cytoplasmic C-terminal tail. Upon ligand binding, cytoplasmic portions of the activated receptor interact with heterotrimeric G-coupled proteins to induce various second messengers, which subsequently activate various signal transduction pathways depending upon the specific G-coupled protein associated with the receptor. Preferred polypeptides of the invention comprise the following amino acid sequence: CFKRKPKREHCSCP
ITYQSLGDILNASFFSKRKGMQEVKLNSYVVS GTIGLKEKISLSEPVFLTFRHN
QPGDKRTKHICVYWEGSEGGRWSTEGCSHVHSNGSYTKCKCFHLSSFAVLV
ALAPKEDPVLTVITQVGLTISLLCLFLAILTFLLCRPIQNTSTSLHLELSLCLFLA
HLLFLTGINRTEPEVLCSIIAGLLHFLYLACFTWMLLEGLHLFTVRNLKVAN
YTSTGRFKKRFMYPVGYGIPAVIIAVSAIVGPQNYGTFTHCWLKLDKGFIWSF
MGPVAVIILINLVFYFQVLWILRSKLSSLNKEVSTIQDTRVMTFKAISQLFILGC
SWGLGFFMVEEVGKTIGSIIAYSFTIINTLQGVLLFVVHCLLNQRQVRMEYKKW

FSGMRKGVETESTEMSRSTTQTKTEEVGKSSEIFHKGGTASSSAESTKQPQPQ
 VHLVSAAWLKMN (SEQ ID NO: 298), and/or FFWKENLRRNGSREDFARRATQ
 LIQSVELSIWNASFASPGKGQISEFDIVYETKRCNETRENAFLEAGNNTMDINC
 ADALKGNLRESTAVALSLINLLGIF SEQ ID NO: 299. Polynucleotides

5 encoding these polypeptides are also provided.

Included in this invention as preferred domains are two EGF-like protein domains, which were identified using the ProSite analysis tool (Swiss Institute of Bioinformatics). First, a sequence of about forty amino-acid residues long found in the sequence of epidermal growth factor (EGF) has been shown to be present in a
 10 large number of membrane-bound and extracellular, mostly animal proteins. Many of these proteins require calcium for their biological function and a calcium-binding site has been found to be located at the N-terminus of some EGF-like domains. Calcium-binding is crucial for numerous protein-protein interactions. We have used the N-terminal part of the EGF domain as a consensus pattern. It includes the negative N-
 15 terminus and the possible hydroxylation site. The consensus pattern is as follows:[DEQN].[DEQN]{2}C.{3,14}C.{3,7}C.[DN].{4}[FY].C [The four C's are involved in disulfide bonds].

Preferred polypeptides of the invention comprise the following amino acid sequence: DINECETGLAKCKYKAYCRNKVGGYIC (SEQ ID NO: 300).
 20 Polynucleotides encoding these polypeptides are also provided. Secondly, post-translational hydroxylation of aspartic acid or asparagine to form erythro-beta-hydroxyaspartic acid or erythro-beta-hydroxyasparagine has been identified in a number of proteins with domains homologous to (EGF). Based on sequence comparisons of the EGF-homology region that contains hydroxylated Asp or Asn, a
 25 consensus sequence located in the N-terminal of EGF-like domains has been identified that seems to be required by the hydroxylase(s). The consensus sequence is as follows: C.[DN].{4}[FY].C.C.

Preferred polypeptides of the invention comprise the following amino acid sequence: CRNKVGGYICSC (SEQ ID NO: 301). Polynucleotides encoding these
 30 polypeptides are also provided.

Further preferred are polypeptides comprising the calcium-binding EGF-like domain and aspartic acid and asparagine hydroxylation site listed above, and at least

5, 10, 15, 20, 25, 30, 50, or 75 additional contiguous amino acid residues of the sequence referenced in Table I for this gene and the embodiments listed herein. The additional contiguous amino acid residues is N-terminal or C-terminal to one or both of the listed domains. Alternatively, the additional contiguous amino acid residues is both N-terminal and C-terminal to one or both of the listed domains, wherein the total N- and C-terminal contiguous amino acid residues equal the specified number. The above preferred polypeptide domains are characteristic of a signature specific to EGF like proteins. Based on the sequence similarity and conserved domains, The translation product of this gene is expected to share at least some biological activities with EGF-like proteins. Such activities are known in the art, some of which are described elsewhere herein.

This gene is expressed primarily in eosinophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic disorders or anemias and leukemias, immunodeficiencies, infection, lymphomas, auto-immunities and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 145 as residues: Ser-22 to Ser-30, Pro-33 to Cys-48, Asp-50 to Lys-67, Pro-117 to Ser-130. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in eosinophils combined with its homology to a known human seven transmembrane domain protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders, particularly considering the fact that the majority of 7 transmembrane receptors are tightly associated with signal transduction pathways which are integral to the modulation of the cell cycle. As such, the protein product of this gene may play a role in the regulation of cellular division, where loss of regulation may result in proliferating cells and the onset of tumors or cancer. Additionally, the expression in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene is useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Similarly, the tissue distribution and homology to CD97 indicates that the protein product of this gene might be a marker for differentiation and activation of eosinophils, and therefore is useful for the diagnosis and treatment of immune disorders including: leukemias, lymphomas, auto-immunities, immunodeficiencies (e.g., AIDS), immuno-suppressive conditions (transplantation) and hematopoietic disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. In addition this gene product is applicable in conditions of general microbial infection, inflammation or cancer. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:32 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
 5 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3266 of SEQ ID NO:32, b is an integer of 15 to 3280, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.

10 **FEATURES OF PROTEIN ENCODED BY GENE NO: 23**

The translation product of this gene has been found to have homology to the rat neural F box protein NFB42, in addition to a conserved *Caenorhabditis elegans* C14B1.3 protein (See, e.g., Genbank Accession Nos. gil3851648|gb|AAC97505.1| (AF098301) and gil558270; all references available through these accessions are
 15 hereby incorporated by reference herein). Preferred polypeptides of the invention comprise the following amino acid sequence: ALCPHPLILNVTVPAPSCRHVK KVVASPPSTTTMIAMDAPHSKAALDSINELPENILLELFTHVPARQLLLNCRL VCSLWRDLIDLMTLWKRKCLREGFITKDWDPVADWKIFYFLRSLHRNLLR NPCAEEDMFAWQIDFNGGDRWKVESLPGAHGTFDPDPKVKKYFVTSYEMCL
 20 KSQVLVDLVAEGYWEELLDTRPDIVVKDWFAARADCGCTYQLKVQLASA DYFVLASFEPPTVTIQQWNNATWTEVSYTFSDYPRGVRYILFQHGGRTQY WAGWYGPRVTNSSIVVSPKMTRNQASSEAQPGQKHGQEEAAQSPYRAVV QIF (SEQ ID NO: 302). Polynucleotides encoding these polypeptides are also provided.

25 The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in immune cells, especially primary dendritic cells, and T cells, and to a lesser extent in a variety of other tissues including breast,
 30 keratinocytes, epididymus (cauda), lung, multiple sclerosis, endometrial stromal cells, IL4 induced umbilical vein endothelial cells, fetal kidney, fetal dura mater, rejected kidney, and osteoblasts.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer and other proliferative disorders, particularly of the immune system or endothelial cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 146 as residues: Pro-41 to Cys-47, Phe-52 to Gly-59, Pro-62 to His-70. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in immune cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product in T-cells indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g., by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities,

such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions and as nutritional supplements. It may also have a very wide range of biological activities although no evidence for any is provided in the specification. Typical of these are cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g., for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of haematopoiesis (e.g., for treating anaemia or as adjunct to chemotherapy); stimulation of growth of bone, cartilage, tendons, ligaments and/or nerves (e.g., for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumours); haemostatic or thrombolytic activity (e.g., for treating haemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g., for treating septic shock, Crohn's Disease); as antimicrobials; for treating psoriasis or other hyperproliferative disease; for regulation of metabolism, behaviour, and many others. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:33 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
 5 formula of a-b, where a is any integer between 1 to 1283 of SEQ ID NO:33, b is an integer of 15 to 1297, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 24

10 The translation product of this gene shares sequence homology with the human, mouse, and bovine dopamine hydroxylase which is thought to be important in the modification of dopamine, a neurotransmitter (See Genbank Accession Nos. gil30474, gil162965, and/or gil2358082; all references available through these
 15 accessions are hereby incorporated by reference herein). Preferred polypeptides of the invention comprise the following amino acid sequence: RQRSWNPQT
 NCYHPNMPDAFLTCTVIFAWAIGGEGFSYPPHVGLSLGTPLDPHYVLLEVH
 YDNPTYEEGLIDNSGLRLFYTMDIRKYDAGVIEAGLWVSLFHTIPPGMPEF
 QSEGHCTLECLEEAEAEKPSGIHVFAVLLHAHLAAGRIRLRHFRKGKEMKL
 LAYDDDFDFNFQEFQYLKEEQTILPGDNLITECRYNTKDRAEMTWGGLSTR
 20 SEMCLSYLLYYPRLNTRCASIPDIMEQLQFIGVKEIYRPVTTWPFIIKSPKQYK
 NLSFMDAMNKFkwTKKEGLSFNKLVLSPVNVRCskTDNAEWSIPRNDsIT
 SRYRKTL (SEQ ID NO: 303). Polynucleotides encoding these polypeptides are also provided.

A preferred polypeptide fragment of the invention comprises the following
 25 amino acid sequence: MCCWPLLLWGLLPgTAAGGSGRTYPhRTLLDSEGK
 YWLGWSQRGSQIAFRLQVRTAGYVGFGFSPTGAMASADIVVGGVAHGR
 PYLQDY FTNANRELKKDAQQDYHLEYAMENSTHTIIEFTRELHTCDINDKS
 ITDSTVRVIWAYHHE DAGEAGPKYHDSNRGtKSLRLLNPEKTSVLSTALPYF
 DLVNQDVPIPNKDTTYWCQMFKIPVFQEKHHVIKVEPVIQRGHESLVHHILL
 30 YQCSNNFNDSVPGIRARIAITPTCPMHSSPV KL (SEQ ID NO: 304).
 Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in brain, the pulmonary system, and to a lesser extent in kidney.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological and behavioral disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, endocrine, or cancerous and wounded tissues) or bodily fluids (e.g., sputum, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 147 as residues: Ser-33 to Trp-38, Gly-40 to Gly-45, Asn-93 to Asp-105, Thr-128 to Thr-137, Glu-150 to Lys-167, Pro-197 to Tyr-203, Cys-242 to Asn-247, Ser-253 to Tyr-258, His-307 to Glu-314, Glu-357 to Gly-362, Trp-373 to Gln-378, Ser-402 to Glu-408. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain and homology to a protein involved in the modification of dopamine indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive

compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Alternatively, the homology to dopamine hydroxylase indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers, particularly Addison's Disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g., diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g., hyper-, hypothyroidism), parathyroid (e.g., hyper-, hypoparathyroidism), hypothalamus, and testes. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:34 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2170 of SEQ ID NO:34, b is an integer of 15 to 2184, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 25

When tested against Jurkat T-cell lines, supernatants removed from cells containing this gene activated the gamma activating sequence (GAS), a promoter element found upstream of many genes which are involved in the Jak-STAT pathway.

The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. Thus, it is likely that
5 this gene activates T-cells through the JakStat signal transduction pathway.

This gene is expressed in a variety of human normal and diseased tissues including breast, infant adrenal gland, skin tumor, colon, pituitary, Wilm's tumor, and to a lesser extent in other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as
10 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast cancer and other proliferative disorders, afflicting endocrine or endothelial tissues. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential
15 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system or of breast and/or breast lymph nodes, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, endocrine, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial
20 fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in breast, infant adrenal gland, skin tumor, colon, pituitary, and Wilm's tumor, and biological activity in activating the GAS promoter
25 element indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers, particularly Addison's Disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g., diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g., hyper-,
30 hypothyroidism), parathyroid (e.g., hyper-, hypoparathyroidism), hypothalamus, and testes. Alternatively, the tissue distribution and biological activity indicates that polynucleotides and polypeptides corresponding to this gene are useful for the

diagnosis and treatment of cancer and other proliferative disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells, (i.e., breast, skin and Wilm's tumors) indicates that this protein may play a role in the regulation of cellular division. Additionally, the expression in hematopoietic cells and tissues

5 indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. In such an event, this gene is useful in the treatment of lymphoproliferative disorders, and in the maintenance and

10 differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Furthermore, the protein may also be used to determine

15 biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:35 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

25 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 935 of SEQ ID NO:35, b is an integer of 15 to 949, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 26

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the
5 following amino acid sequence: TGTFWSPRSQRRGCCGRRAPRPEAMENGAVYS
PTTEEDPGPARGPRSGLAAYFFMGRLPLLRVLKGLQLLSLLAFICEEVVSQ
CTLCGGLYFFEFVSCSAFLLSLLILIVYCTPFYERVDTTKVKSSDFYITLTGTGCV
FLLASIIFVSTHDRTSAEIAAIVFGFIASFMLLDFTMLYEKRQESQLRKPENTT
RAEALTEPLNA (SEQ ID NO: 305). Polynucleotides encoding these polypeptides
10 are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

This gene is expressed primarily in dendritic cells, and to a lesser extent in
15 melanocytes, fetal liver and spleen and several other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation, and disorders of the hepatic and immune systems.
20 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., hematopoietic,
25 hepatic, immune, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 149 as residues: Phe-63 to Ser-75, Thr-97 to Ser-102, Glu-128 to Arg-143. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product in dendritic cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the tissue distribution in fetal liver indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g., hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Furthermore, the protein may also be used to determine biological activity, raise

antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:36 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3324 of SEQ ID NO:36, b is an integer of 15 to 3338, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 27

In a specific embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the
20 following amino acid sequence: ASAPRVMRGLAGFPALSGLASVCLWATFSA QLPGPVAATSWTPAPLGCSAARSGPEKRLGTAAPGSAASLAQAGPGAPCRV LPVDPAPAALNVREPGWLGGFLFDGALLQVLLNFLRKSTDVLMDTREAESLEV E (SEQ ID NO: 306).

In another embodiment polypeptides of the invention comprise the following
25 amino acid sequence: NKLHSFPVFLSQLLLDRQLLHAPQTLPTPHCGGSSRP GP SHPPWLLIQLPCVHVALWQMLRDFSDSRITPSTLTTQPAAQTAAPAKDQES DIVGGEGILCDIAFLQEDHPLGVGGASAPSSRRELSRRGVHTQTLPEDGTLHG TPSSSFDGCIKYIISWPLAPGCDLPSLELSLVCKGVSSCMGFAAG (SEQ ID NO: 307). Polynucleotides encoding these polypeptides are also provided.

30 This gene is expressed primarily in endothelial cells, lung, and fetal kidney, and to a lesser extent in epididymis, keratinocytes and cerebellum.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cardiovascular diseases involving endothelial cell disturbances such as atherosclerosis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cardiovascular, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 150 as residues: Arg-47 to Leu-54. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in endothelial cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosing and treating disorders of endothelial cells such as atherosclerosis, vasculitis, cardiovascular disease, and emphysema. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions and as nutritional supplements. The polypeptide may possess a wide range of undetected biological activities. Typical of these are cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g., for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of haematopoiesis (e.g., for treating anaemia or as adjunct to chemotherapy); stimulation of growth of bone, cartilage, tendons, ligaments and/or nerves (e.g., for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g., for treating infections, tumours); haemostatic or

thrombolytic activity (e.g., for treating haemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g., for treating septic shock, Crohn's Disease); as antimicrobials; for treating psoriasis or other hyperproliferative disease; for regulation of metabolism, behaviour, and many others. Also contemplated is the use of the
5 corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
10 related to SEQ ID NO:37 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
15 formula of a-b, where a is any integer between 1 to 1549 of SEQ ID NO:37, b is an integer of 15 to 1563, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 28

20 In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: PGRPTRPTKNKVCVCLGMLFWAYPICVFIDSL SCQPCLWSTGATSHFNSPTTSPLFTLFMPCALAPNPFT QLGLDDR (SEQ ID
25 NO: 308). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in meningima.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
30 not limited to, tumors or disorders of the central nervous system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For

a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 151 as residues: His-29 to Thr-34. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in meningioma indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception, as well as disorders of the meninges such as meningioma and meningitis. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:38 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1034 of SEQ ID NO:38, b is an integer of 15 to 1048, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 29

The translation product of this gene has been shown to encode a human brain specific mitochondrial carrier (Genbank Accession No. gil3851540|gb|AAD04346.1| (AF078544); all references available through this accession are hereby incorporated herein by reference) which shares sequence homology with the human body weight disorder associated gene C5 product which is known to be differentially expressed in obese compared to lean mice (See GeneSeq Accession No. R91281). Based on the sequence similarity, the translation product of this gene is expected to share at least some biological activities with mitochondrial carriers proteins. Such activities are known in the art, some of which are described in Sanchis et al, J. Biol. Chem. 273:34611-34615 (1998), incorporated herein by reference.

Included in this invention as preferred domains are mitochondrial energy transfer protein (METP) domains, which were identified using the ProSite analysis tool (Swiss Institute of Bioinformatics). Structurally, members of the family of mitochondrial energy transfer proteins consist of three tandem repeats of a domain of approximately one hundred residues. Each of these domains contains two transmembrane regions. As a signature pattern, we selected one of the most conserved regions in the repeated domain, located just after the first transmembrane region. To detect this widespread family of proteins, a consensus sequence was developed that contains the most conserved regions in the repeated domain. The consensus pattern is as follows: P.[DE].[LIVAT].[RK].[LRH].[LIVMFY].[QMAIGV].

Preferred polypeptides of the invention comprise the following amino acid sequences: PVDLTCTRLQ (SEQ ID NO: 309) and PTDVLKIRMQ (SEQ ID NO: 310). Polynucleotides encoding these polypeptides are also provided.

Further preferred are polypeptides comprising the METP domains of the
5 sequence listed above, and at least 5, 10, 15, 20, 25, 30, 50, or 75 additional
contiguous amino acid residues of the sequence referenced in Table I for this gene.
The additional contiguous amino acid residues is N-terminal or C-terminal to the
METP domain. Alternatively, the additional contiguous amino acid residues is both
N-terminal and C-terminal to the METP domain, wherein the total N- and C-terminal
10 contiguous amino acid residues equal the specified number. The above preferred
polypeptide domain is characteristic of a signature specific to mitochondrial energy
transfer proteins.

The gene encoding the disclosed cDNA is believed to reside on chromosome
X. Accordingly, polynucleotides related to this invention are useful as a marker in
15 linkage analysis for chromosome X.

This gene is expressed primarily in brain, and to a lesser extent, in T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as
reagents for differential identification of the tissue(s) or cell type(s) present in a
biological sample and for diagnosis of diseases and conditions which include, but are
20 not limited to, neurological and behavioral disorders and immune disorders and/or
obesity. Similarly, polypeptides and antibodies directed to these polypeptides are
useful in providing immunological probes for differential identification of the
tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,
particularly of the digestive, immune, and nervous systems, expression of this gene
25 at significantly higher or lower levels is routinely detected in certain tissues or cell
types (e.g., immune, neural, or cancerous and wounded tissues) or bodily fluids (e.g.,
lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell
sample taken from an individual having such a disorder, relative to the standard gene
expression level, i.e., the expression level in healthy tissue or bodily fluid from an
30 individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 152 as residues: Gln-189 to Gly-195. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain and homology to mitochondrial carrier proteins indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:39 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 1416 of SEQ ID NO:39, b is an integer of 15 to 1430, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 30

Preferred polypeptides of the invention comprise the following amino acid sequence: MTFGSTISPTSTHASPSLGFCSSWLLLEDLEEQLYCSAFEEAALTR
RICNPTSCWLPLDMELLHRQVLA¹QTQRVLLGMWLRRAWDTWVSPRRVAP
GSRCLLTASHPCTEKRRKASAXQRNLGYPLAMLCLLVLTGLSVLIVAIHILEL
10 LIDEAAMP¹⁰PRGMQGTSLGQVSFSKLGSGFAVIQVVLIFYLMVSSVVG¹⁰GFYSSPLF
RSLRPRWHD¹⁰TAMTQIIGNCVCLLVLSSALPVFSRTLGLTRFDLLGDFGRFNWL
GNFYIVFLYNA¹⁰AFAGLTTLCLVKTF¹⁰TAAVRAELIRAFGLDRLPLPVSGFPQAS
RKTQHQ (SEQ ID NO: 311). Polynucleotides encoding such polypeptides are also provided.

15 This gene is expressed primarily in immune system tissues (e.g. resting T-cells, primary dendritic cells, and neutrophils, apoptotic T-cells) and umbilical vein. This gene is expressed to a lesser extent in the gastrointestinal tissue (e.g. small intestine, colon), brain (e.g. cerebellum, frontal cortex), aorta endothelial cells, skin tumor, embryonic tissue, thymus, and cancers (e.g. cheek, breast, synovial).

20 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer and immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for
25 differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and gastrointestinal tract expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, gastrointestinal, cancerous and wounded tissues) or bodily fluids (e.g., amniotic, serum, plasma, urine, synovial fluid and
30 spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 153 as residues: Asp-21 to Ser-29. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in immune cells (e.g. T-cells, dendritic cells,
5 neutrophils) indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the
10 proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene
15 product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and
20 tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits
25 hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The tissue distribution in skin tumors and cancerous tissue (e.g. cheek, breast, synovial sarcoma) indicates that polynucleotides and polypeptides corresponding to this gene are useful for the
30 diagnosis and treatment of cancer and other proliferative disorders. Expression in cellular sources such as embryonic tissue marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Additionally, the

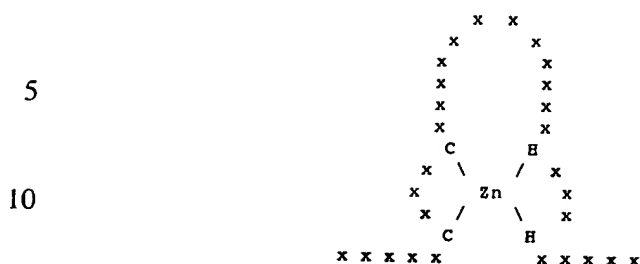
expression in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene is useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from
5 early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or
10 immunotherapy targets for the above listed tissues. The tissue distribution in cerebellum and frontal cortex indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative
15 Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction,
20 aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.
25 Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional
30 supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:40 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2089 of SEQ ID NO:40, b is an integer of 15 to 2103, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 31

The polypeptide of this gene has been determined to have a zinc finger (Zinc finger, C2H2 type) domain at about amino acid position 16-50 of the amino acid sequence referenced in Table 1 for this gene. Therefore,

A preferred polypeptide fragment of the invention comprises the following amino acid sequence: LCVCLVYLCMYGVCLCVIVCVSGVSLCLYVWGV SVC DCVSVFMCVCLCVIFCVY GKPRTEHYHSPHLAKQKAFREMCGRHDVSAAGIF QSYV (SEQ ID NO: 312). Polynucleotides encoding these polypeptides are also provided. 'Zinc finger' domains are nucleic acid-binding protein structures first identified in the *Xenopus* transcription factor TFIIIA. These domains have since been found in numerous nucleic acid-binding proteins. A zinc finger domain is composed of 25 to 30 amino-acid residues. There are two cysteine or histidine residues at both extremities of the domain, which are involved in the tetrahedral coordination of a zinc atom. It has been proposed that such a domain interacts with about five nucleotides. A schematic representation of a zinc finger domain is shown below:



Many classes of zinc fingers are characterized according to the number and positions of the histidine and cysteine residues involved in the zinc atom coordination. In the first class to be characterized, called C2H2, the first pair of zinc coordinating residues are cysteines, while the second pair are histidines. A number of experimental reports have demonstrated the zinc- dependent DNA or RNA binding property of some members of this class. Some of the proteins known to include C2H2-type zinc fingers are listed below. We have indicated, between brackets, the number of zinc finger regions found in each of these proteins; a '+' symbol indicates that only partial sequence data is available and that additional finger domains is present.

This gene is expressed primarily in salivary gland.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, salivary gland related diseases, diseases of the mouth, and other digestive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., saliva, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 154 as residues: Gly-46 to His-54. Polynucleotides encoding said polypeptides are also provided.

5 The tissue distribution indicates that the protein products of this gene are useful for diagnosis and treatment of salivary gland related diseases (mumps, calculi formation in ducts, sarcoidosis, facial palsy, tumors, Sjogrens Syndrome) and other digestive system disorders. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a
10 nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
15 related to SEQ ID NO:41 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
20 formula of a-b, where a is any integer between 1 to 2335 of SEQ ID NO:41, b is an integer of 15 to 2349, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 32

25 This gene is expressed primarily in fetal tissue (e.g. spleen, liver, brain), cancerous tissues (e.g. ovarian, colon, stomach, parathyroid) and to a lesser extent in immune cells and tissue (e.g. B-cells, T-cells, bone marrow), and reproductive organs.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a
30 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer, particularly of the colon and ovaries, disorders of the developing fetus, neurodegenerative conditions, and immune system disorders.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is
5 routinely detected in certain tissues or cell types (e.g., immune, reproductive, neural, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 155 as residues: Lys-35 to Lys-47. Polynucleotides encoding said polypeptides are also provided.

The expression of this gene within fetal tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular
15 division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern
20 formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of
25 potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types
30 of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in

modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. The tissue distribution in immune cells (such as T-cells and B-cells) and immune tissues (bone marrow) indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The tissue distribution in parathyroid indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers. Representative uses are described in the "Biological Activity", "Hyperproliferative Disorders", and "Binding Activity" sections below, in Example 11, 17, 18, 19, 20 and 27, and elsewhere herein. Briefly, the protein can be used for

the detection, treatment, and/or prevention of Addison's Disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism), hypothalamus, and testes. Additionally, the tissue distribution in brain tissue indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:42 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1545 of SEQ ID NO:42, b is an integer of 15 to 1559, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.

5

FEATURES OF PROTEIN ENCODED BY GENE NO: 33

When tested against U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells through the Jak-STAT signal transduction pathway. The gamma
10 activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and
15 differentiation of cells.

This gene is expressed primarily in skin tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
20 not limited to, skin disorders, particularly skin cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skin, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell
25 types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 156 as residues: Pro-38 to Gly-44, Phe-56 to Thr-64. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in skin indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. 5 keratoses, Bowen's Disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's Disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, 10 pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. Moreover, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athletes foot, and ringworm). Protein, as well as, antibodies directed against the 15 protein may show utility as a tumor marker and immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:43 and may have been publicly available prior to conception of 20 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1752 of SEQ ID NO:43, b is an 25 integer of 15 to 1766, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 34

The translation product of this gene shares sequence homology with mitogen- 30 induced prostate carcinoma (mouse) which is thought to be important in the etiology of cancer. In this respect, this gene is mitogen-induced and/or involved in cell proliferation.

Preferred polypeptides of the invention comprise the following amino acid sequence: GHMPYGWLTEIRAVYPAFDKNNPSNKLVSTSNTVTAAHIKKF
TFVCMALSLTLCFVMFWTPNVSEKILIDIIGVDFAFAELCVVPLRIFSFFPVPT
VRAHLTGWMLTLKKTFLAPSSVLRIIVLIASLVVLPYLGVBHGATLGVGSLLA
5 GFVGESTMVAIAACYVYRKQKKKMENESATEGEDSAMTDMPTTEEVTDIVE
MRENE (SEQ ID NO: 313) and/or QVVFVAILLHSHLECREPLLIPILSLYMGA
LVRCTTLCLGYYKNIHDIIPDRSGPELGGDATIRKMLSFWWPLALILATQRISR
PIVNLFVSRDLGGSSAATEAVAILTATYPV (SEQ ID NO: 314). Polynucleotides
encoding these polypeptides are also provided.

10 The gene encoding the disclosed cDNA is believed to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

This gene is expressed primarily in early infant and adult brain, retina, fetal tissue (e.g., liver, spleen, whole embryo) and to a lesser extent in immune cells (e.g.,
15 monocytes and T-cells), colon, and parathyroid tumor tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancers, disorders of the immune system and nervous system.
20 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the metabolic system (cancers), expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, neural,
25 cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic
30 epitopes shown in SEQ ID NO: 157 as residues: Arg-122 to Ser-139, Met-144 to Glu-149. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution and homology to mitogen induced prostate carcinoma (mouse) indicates that polynucleotides and polypeptides corresponding to this gene are useful for the study and treatment of cancers, including but not limited to the colon, parathyroid, and adrenal glands. Moreover, the expression within fetal tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. The tissue distribution in immune cells (T-cells, monocytes) indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or

activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

- 5 Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory
10 bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that
15 influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The tissue distribution in brain indicates polynucleotides and polypeptides corresponding to this gene are
20 useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease,
25 Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism,
30 and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to
5 identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
10 related to SEQ ID NO:44 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
15 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2558 of SEQ ID NO:44, b is an integer of 15 to 2572, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 35

20 This gene is expressed primarily in adult pulmonary tissue, umbilical vein, prostate, and fetal tissue (e.g., heart).

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
25 not limited to, diseases of the pulmonary system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the pulmonary system, expression of this gene at significantly higher or lower levels is routinely detected in
30 certain tissues or cell types (e.g., pulmonary, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the

standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 158 as residues: Arg-45 to Gly-51, Glu-75 to Asn-81.

5 Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in pulmonary tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of disorders associated with developing lungs, particularly in premature infants where the lungs are the last tissues to develop. Additionally, the tissue distribution indicates
10 that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and intervention of lung tumors, since the gene is involved in the regulation of cell division, particularly since it is expressed in fetal tissue. Moreover, the expression within fetal tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may
15 show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

20 Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have
25 applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue
30 differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in

proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:45 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 512 of SEQ ID NO:45, b is an integer of 15 to 526, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 36

This gene is expressed primarily in adipose tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, fat metabolism. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the metabolic system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,

the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 159 as residues: Pro-96 to Ser-106. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in adipose tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment of obesity and other metabolic and endocrine conditions or disorders. Furthermore, the protein product of this gene may show utility in ameliorating conditions which occur secondary to aberrant fatty-acid metabolism (e.g. aberrant myelin sheath development), either directly or indirectly. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:46 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1018 of SEQ ID NO:46, b is an integer of 15 to 1032, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:46, and where b is greater than or equal to a + 14.

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 37

This gene is expressed primarily in adult brain tissue, testes, placenta, kidney, infant and fetal tissue (e.g., liver, spleen, lung) and to a lesser extent in immune cells (e.g., T-cells and neutrophils) and in cancerous tissues (e.g., ovarian tumor, Hodgkins lymphoma, pancreas, T-cell).

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, CNS disorders, disorders of the testicles, cancer, particularly ovarian, pancreatic, T-cell, and Hodgekin's lymphoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, CNS, and testes expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, urogenital, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the expression within fetal tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders"

and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities,

such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Additionally, the tissue distribution in testes indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that is expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product is expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:47 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2666 of SEQ ID NO:47, b is an integer of 15 to 2680, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where b is greater than or equal to a + 14.

5

FEATURES OF PROTEIN ENCODED BY GENE NO: 38

When tested against fibroblast cell lines, supernatants removed from cells containing this gene activated the EGR1 assay. Thus, it is likely that this gene activates fibroblast cells through a signal transduction pathway. Early growth response 1 (EGR1) is a promoter associated with certain genes that induces various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation.

This gene is expressed primarily in endometrial stromal cells, endometrial tumors, keratinocytes, fetal tissue (e.g. liver, spleen) and to a lesser extent in endothelial cells and immune cells (e.g., T-cells).

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endometrial carcinoma and immune cells disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the female reproductive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in the endometrium indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating female infertility. The protein product is likely involved in preparation of the endometrium of implantation and could be administered either topically or orally. Alternatively, this gene could be

transfected in gene-replacement treatments into the cells of the endometrium and the protein products could be produced. Similarly, these treatments could be performed during artificial insemination for the purpose of increasing the likelihood of implantation and development of a healthy embryo. In both cases this gene or its gene product could be administered at later stages of pregnancy to promote healthy development of the endometrium. Additionally, polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of endometrial carcinoma. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Additionally, the expression in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene is useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. The tissue distribution in immune cells such as helper T-cells indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders.

Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein.

Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such

as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The tissue distribution in keratinocytes indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment, diagnosis, and/or prevention of various skin disorders. Representative uses are described in the "Biological Activity", "Hyperproliferative Disorders", "infectious disease", and "Regeneration" sections below, in Example 11, 19, and 20, and elsewhere herein. Briefly, the protein is useful in detecting, treating, and/or preventing congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's Disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's Disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, and ringworm). Moreover, the protein product of this gene may also be useful for the treatment or diagnosis of various connective tissue disorders (i.e., arthritis, trauma, tendonitis, chondromalacia and inflammation, etc.), autoimmune disorders (i.e., rheumatoid arthritis, lupus, scleroderma, dermatomyositis, etc.), dwarfism, spinal deformation, joint abnormalities, and

chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents
5 that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences; such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
10 related to SEQ ID NO:48 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
15 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1716 of SEQ ID NO:48, b is an integer of 15 to 1730, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 39

20 This gene is expressed primarily in LNCAP cells (prostate cell line) and retina derived N2b5HR cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
25 not limited to, prostate cancer and eye disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male urogenital and reproductive system expression of this gene at significantly higher or lower levels is
30 routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative

to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 162 as residues: Asn-50 to Ser-57. Polynucleotides
5 encoding said polypeptides are also provided.

The expression in prostate may indicate the gene or its products can be used in the disorders of the prostate, including inflammatory disorders, such as chronic prostatitis, granulomatous prostatitis and malacoplakia, prostatic hyperplasia and prostate neoplastic disorders, including adenocarcinoma, transitional cell carcinomas, ductal carcinomas, squamous cell carcinomas, or as hormones or factors with systemic or reproductive functions. The tissue distribution in retina indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or detection of eye disorders including blindness, color blindness, impaired vision, short and long sightedness, retinitis pigmentosa, retinitis proliferans, and retinoblastoma, retinochoroiditis, retinopathy and retinoschisis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:49 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1261 of SEQ ID NO:49, b is an integer of 15 to 1275, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:49, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 40

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the
5 following amino acid sequence: RCCCRGCSCRARLCPPARSTAVAPECRGAHPSR
AMRPGTALQAVLLAVLLVGLRAATGRLLSGQPVCRRGTQRPCYKVIYFHD
TSRRLNFEEAKEACRRGWRPASQHRVLKMNRN (SEQ ID NO: 315).

Polynucleotides encoding these polypeptides are also provided.

A preferred polypeptide fragment of the invention comprises the following
10 amino acid sequence: MRPGTALQAVLLAVLLVGLRAATGRLLSGQPVCRRG
TQRPCYKVIYFHDTSRRLNFEEAKEACRRGWRPASQHRVLKMNRN (SEQ ID
NO: 316). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in smooth muscle and human thyroid and to a
15 lesser extent in amniotic cells and human endometrial stromal cells-treated with
progesterone.

Therefore, polynucleotides and polypeptides of the invention are useful as
reagents for differential identification of the tissue(s) or cell type(s) present in a
biological sample and for diagnosis of diseases and conditions which include, but are
not limited to, thyroid disorders. Similarly, polypeptides and antibodies directed to
20 these polypeptides are useful in providing immunological probes for differential
identification of the tissue(s) or cell type(s). For a number of disorders of the above
tissues or cells, particularly of the endocrine system, expression of this gene at
significantly higher or lower levels is routinely detected in certain tissues or cell types
(e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine,
25 synovial fluid and spinal fluid) or another tissue or cell sample taken from an
individual having such a disorder, relative to the standard gene expression level, i.e.,
the expression level in healthy tissue or bodily fluid from an individual not having the
disorder.

Preferred polypeptides of the present invention comprise immunogenic
30 epitopes shown in SEQ ID NO: 163 as residues: Ser-75 to Leu-81. Polynucleotides
encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of endocrine disorders of the thyroid.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:50 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1748 of SEQ ID NO:50, b is an integer of 15 to 1762, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:50, and where b is greater than or equal to a + 14.

15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 41**

This gene is expressed primarily in human testes tumor and bone marrow.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the testicles including but not limited to testicular cancer and immune system disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system and immune system expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, immune, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 164 as residues: His-31 to Gly-41. Polynucleotides encoding said polypeptides are also provided.

5 The tissue distribution in testes, particularly testicular tumors, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) 10 are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that is expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product is expressed in other specific tissues or organs where it may play related functional roles in other processes, such as 15 hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. The tissue distribution in bone marrow indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in 20 Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the 25 treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory 30 bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity

disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits

5 hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their

10 interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

15 related to SEQ ID NO:51 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

20 formula of a-b, where a is any integer between 1 to 2045 of SEQ ID NO:51, b is an integer of 15 to 2059, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 42

25 The translation product of this gene shares sequence homology with protocadherins, which are related to cadherin, and possess cell adhesive ability. Cadherins are glycosylated integral membrane proteins that are involved in cell-cell adhesion.

This gene is expressed primarily in brain (infant, adult frontal lobe, manic

30 depression tissue) and to a lesser extent in epididymus, healing groin wounds, ovary, adipocytes, and fetal tissue (e.g., kidney and retina).

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative disorders, impaired male and female fertility, developmental disorders, fibrosis, and manic depression. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system and reproductive system expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 165 as residues: Val-35 to Lys-41, Ser-68 to Gln-73, Glu-88 to Glu-93, Arg-156 to Gly-163, Ala-199 to Gly-206, Asp-216 to Ser-226, Thr-249 to Asn-254, Asp-339 to Pro-345, Ile-370 to Gly-379, Pro-429 to Glu-434, Arg-461 to Pro-466, Ala-475 to Thr-482, Pro-585 to Gly-593, Glu-631 to Gln-639, Pro-674 to Pro-682, Gln-715 to Gly-720, Ser-736 to Arg-742. Polynucleotides encoding said polypeptides are also provided.

BLAST analysis reveals high homology to protocadherin sequences. These sequences are related to cadherin, and possess cell adhesive ability. Such proteins may have regulatory functions in the cell, as well as the cell-cell adhesive properties. Antibodies produced against these sequences are useful for modulating the binding activity of these protocadherins, and can be used therapeutically. The tissue distribution in brain indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease,

Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive
5 disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation,
10 neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. The tissue distribution in epididymus indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment
15 of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that is expressed, particularly at low levels, in other tissues
20 of the body. Therefore, this gene product is expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Moreover, the expression within fetal tissue (e.g., kidney and retina) and other cellular sources marked by proliferating cells indicates this
25 protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including blindness, cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions
30 involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent

of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:52 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3268 of SEQ ID NO:52, b is an integer of 15 to 3282, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where b is greater than or equal to a + 14.

30 FEATURES OF PROTEIN ENCODED BY GENE NO: 43

Preferred polypeptides of the invention comprise the following amino acid sequence:

IRHEQQGEEDDEHARPLAESLLLAIALDLLFCPDFTVQSHRRSTVDSAEDVHSL
DSCEYIWEAGVGFAHSPQPNYIHDMNRMELLKLLLTCTFSEAMYLPPAPESGS
TNPWVQFFCSTENRHALPLFTSLLNTVCAYDPVGYGIPYNHLLFSDYREPLVE
EAAQVLIVTLDDHDSASSASPTVDGTTTGTAMDDADPPGPENLFVNYLSRIHRE
5 EDFQFILKGIARLLSNPLLQTYLPNSTKKDPVPPGAASSLLEALRLQEQEIPLLRA
EEQRRPRHPCPHLLPQRCPGRSV (SEQ ID NO: 317). Polynucleotides encoding
such polypeptides are also provided.

This gene is expressed primarily in brain, breast, breast cancer tissue and to a
lesser extent in epididymus, amniotic cells, and embryo tissue.

10 Therefore, polynucleotides and polypeptides of the invention are useful as
reagents for differential identification of the tissue(s) or cell type(s) present in a
biological sample and for diagnosis of diseases and conditions which include, but are
not limited to, neurodegenerative disorders, impaired CNS function, male sterility,
and breast cancer. Similarly, polypeptides and antibodies directed to these
15 polypeptides are useful in providing immunological probes for differential
identification of the tissue(s) or cell type(s). For a number of disorders of the above
tissues or cells, particularly of the nervous and reproductive systems, expression of
this gene at significantly higher or lower levels is routinely detected in certain tissues
or cell types (e.g., neural, male reproductive, cancerous and wounded tissues) or
20 bodily fluids (e.g., amniotic, serum, plasma, urine, synovial fluid and spinal fluid) or
another tissue or cell sample taken from an individual having such a disorder, relative
to the standard gene expression level, i.e., the expression level in healthy tissue or
bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic
25 epitopes shown in SEQ ID NO: 166 as residues: Pro-22 to Pro-31, Ser-38 to His-43,
Asp-74 to Leu-79, Asp-113 to Glu-121, Leu-157 to Val-166, Ala-189 to Arg-196,
Gln-206 to Arg-211. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain, particularly in the cerebellum, indicates
polynucleotides and polypeptides corresponding to this gene are useful for the
30 detection, treatment, and/or prevention of neurodegenerative disease states, behavioral
disorders, or inflammatory conditions. Representative uses are described in the
"Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11,

15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal
5 cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in
10 normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. The tissue distribution in epididymus indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of
15 conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment
20 and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that is expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product is expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few
25 possible target indications. The expression in the breast tissue may indicate its uses in the diagnosis and/or treatment of breast neoplasia and breast cancers, such as fibroadenoma, papillary carcinoma, ductal carcinoma, Paget's Disease, medullary carcinoma, mucinous carcinoma, tubular carcinoma, secretory carcinoma and apocrine carcinoma, as well as juvenile hypertrophy and gynecomastia, mastitis and
30 abscess, duct ectasia, fat necrosis and fibrocystic diseases. Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may

show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions
5 involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of
10 potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types
15 of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new
20 insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or
25 immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:53 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
30 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 1846 of SEQ ID NO:53, b is an integer of 15 to 1860, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 44

Contact of cells with supernatant expressing the product of this gene increases the permeability of monocytes to calcium. Thus, it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product of this gene binds a receptor on the surface of the monocyte cell. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating monocyte cells.

This gene is expressed primarily in CD34 positive cells derived from human cord blood.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic disorders; immune dysfunction; defects in hematopoietic stem and progenitor cells; susceptibility to chemotherapy and irradiation. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 167 as residues: Ala-38 to Leu-59, Ala-63 to Thr-71, Lys-82 to Leu-91, Glu-97 to Ser-107, Gln-143 to Ala-149, Ile-153 to Leu-158, Ser-169 to Arg-182. Polynucleotides encoding said polypeptides are also provided.

Elevated expression of this gene product in CD34 positive hematopoietic cells indicates that it is expressed by early stem and progenitor cells of the hematopoietic lineages. Therefore, this may represent a soluble factor that is able to control the survival, proliferation, differentiation, or activation of all hematopoietic lineages, including stem and progenitor cells. Thus, it could be quite useful, for example, in ex vivo expansion of stem cell numbers for hematopoietic disorders or for cancer patients. Alternately, it may represent a factor that influences the hematopoietic microenvironment by affecting stromal cells that release other factors required for hematopoietic development. Additionally, the tissue distribution in CD34 positive cells also indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:54 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 756 of SEQ ID NO:54, b is an integer of 15 to 770, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 45

This gene is expressed primarily in breast and 12-week old human embryos and to a lesser extent in stomach cancer and liver.

5 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast cancer; stomach cancer; embryonic defects; hepatic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in
10 providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive and endocrine systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal
15 fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that the protein products of this gene are useful for the diagnosis and/or treatment of a variety of disorders. Elevated expression
20 of this gene product in stomach cancer indicates it is useful as a marker or therapeutic target for stomach cancer. Alternately, expression in breast tissue is influenced by the presence or absence of breast cancer tissue, and may thus also serve as a diagnostic marker for this cancer as well. Expression in the developing embryo may correlate with the normal development of human embryos, and expression in the liver is
25 involved in the regulation of normal liver function and/or liver regeneration.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:55 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
30 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 1079 of SEQ ID NO:55, b is an integer of 15 to 1093, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 46

This gene is expressed primarily in human hypothalamus derived from a patient with schizophrenia.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, schizophrenia; neurological disorders; impaired nervous system function. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 169 as residues: Glu-34 to Trp-39. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain, particularly in the hypothalamus, indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal

cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated
5 expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity,
10 to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
15 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:56 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
20 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 618 of SEQ ID NO:56, b is an integer of 15 to 632, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where b is greater than or equal to a + 14.

25 **FEATURES OF PROTEIN ENCODED BY GENE NO: 47**

The translation product of this gene shares sequence homology with human lecithin-cholesterol acyltransferase (LCAT), which catalyses the transfer of fatty acid from the sn-2 position of lecithin to the free hydroxyl group of cholesterol. Preferred polypeptides of the invention comprise the following amino acid sequence: RLVYN
30 KTSRATQFPDGVDRVPGFGKTFSLFLDPSKSSVGSYFHTMVESLVGWGYT
RGEDVRGAPYDWRRAPNENGPYFLALREMIEEMYQLYGGPVVLVAHSMGN
MYTLYFLQRQPQAWKDKYIRAFVSLGAPWGGVAKTLRVLASGDNNRIPVIG

PLKIREQQRSAVSTSWLLPYNYTWSPEKVVFVQTPTINYTLRDYRKFFQDIGFE
DGWLMRQDTEGLVEATMPPGVQLHCLYGTGVPTPDSFYYESFPDRDPKICFG
DGDGTVNLKSALQCQAWQSRQEHQVLLQELPGSEHIEMLANATTLAYLKRV
LLGP (SEQ ID NO: 318). Polynucleotides encoding such polypeptides are also

5 provided.

This gene is expressed primarily in osteoblasts & dendritic cells and to a lesser extent in muscle and other hematopoietic cell lineages.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a
10 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic disorders; immune dysfunction; osteoporosis; osteopetrosis; muscle degeneration. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential
15 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal and immune systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,
20 the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 170 as residues: Cys-65 to Ser-71. Polynucleotides encoding said polypeptides are also provided.

25 The tissue distribution and homology to lecithin-cholesterol acyltransferase (LCAT) indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of a variety of disorders. For example, atherosclerosis is a pathological condition of mammals characterised by the accumulation of cholesterol in the arteries, which leads to heart disease, strokes, heart
30 attacks and peripheral vascular disease. The enzyme could be used in a novel method of treating atherosclerosis, which involves increasing the level of LCAT activity, which then causes a decrease in the accumulation of cholesterol. The method and the

products can be used for the prophylaxis and treatment of atherosclerosis, and associated heart disease, myocardial infarction, stroke and peripheral vascular disease, as well as individuals suffering from Fish Eye Syndrome (caused by LCAT deficiency) or Classic LCAT Deficiency Syndrome. Alternately, elevated expression
5 of this gene product in osteoblasts and hematopoietic cell lineages indicates that it may play additional roles in bone turnover, regulation of immune system function, and muscular function.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
10 related to SEQ ID NO:57 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
15 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2673 of SEQ ID NO:57, b is an integer of 15 to 2687, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 48

20 When tested against HELA epithelial cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates epithelial cells through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a
25 large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in adult brain, infant brain, fibroblasts,
30 embryonic and fetal tissue (e.g., spleen, liver), placenta and to a lesser extent in endocrine organs, cancerous colon and breast.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, dementia, epilepsy, schizophrenia, and developmental abnormalities.

5 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neural system, endocrine system, and during development, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types

10 (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

15 The tissue distribution in brain indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly,

20 the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive

25 compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation,

30 neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. In addition, the expression of this gene product in synovium (synovial sarcoma) would suggest a role in the detection and treatment of disorders and

conditions afflicting the skeletal system, in particular osteoporosis, bone cancer, connective tissue disorders (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation). The protein is also useful in the diagnosis or treatment of various autoimmune disorders (i.e., rheumatoid arthritis, lupus, scleroderma, and dermatomyositis), dwarfism, spinal deformation, joint abnormalities, and chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid, etc.). The tissue distribution in endocrine tissues indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers. Representative uses are described in the "Biological Activity", "Hyperproliferative Disorders", and "Binding Activity" sections below, in Example 11, 17, 18, 19, 20 and 27, and elsewhere herein. Briefly, the protein can be used for the detection, treatment, and/or prevention of Addison's Disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism), hypothalamus, and testes. Additionally, the expression within fetal tissue, cancerous colon and breast, and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the

polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of
5 degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue
10 markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
15 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:58 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
20 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 605 of SEQ ID NO:58, b is an integer of 15 to 619, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where b is greater than or equal to a + 14.

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 49

Preferred polypeptides of the invention comprise the following amino acid sequence or a subfragment thereof: MNKEDKVWNDCKGVNKLTNLEEQYIILIFQ
NGLDPPANMVFESIINEIGIKNNISNFFAKIPFEEANGRLVACTRITYEESIKGSC
GQKENKIKTVSFESKIQLRSKQEFQFFDEEEETGENHTIFIGPVEKLIVYPPPPA
30 KGGISVTNEDLHCLNEGEFLNDVIIDFYLYLVLEKLKKEDADRIHIFSSFFYK
RLNQRERRNHETTNSIQQKRHGRVKTWTRHVDIFEKDFIFVPLNEAAHWFL
AVVCFFGLEKPKYEPNPHYHENA VIQKCSTVEDSCISSASSEMESCSQNSSAK

PVIKKMLNKKHCIAVIDSNPGQEESDPYKRNICSVKYSVKKINHTASENEEF
NKGESTSQKS (SEQ ID NO: 319). Polynucleotides encoding such polypeptides are also provided.

5 This gene is expressed primarily in fetal tissue, stomach, brain, endometrial cells, and bone and to a lesser extent in prostate, retina, adipocytes, smooth muscle, and tumors of the endometrium, ovaries, and parathyroid.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
10 not limited to, disorders of the endocrine system, ulcers, stomach cancer, epilepsy, schizophrenia, dementia, bone growth, developmental disorders and resorption. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the
15 digestive system and neural systems expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, endocrine system, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression
20 level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions.
25 Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia,
30 trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS,

psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation,
5 neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Expression of this gene product in stomach tissue indicates involvement in digestion, processing, and elimination of food, as well as a potential role for this gene as a diagnostic marker or causative agent in the development of stomach cancer, and cancer in general. The expression within embryonic, fetal tissue and other cellular
10 sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere
15 herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain
20 neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating,
25 detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in
30 proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. The tissue distribution in parathyroid tumor indicates polynucleotides and polypeptides corresponding to this

gene are useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers. Representative uses are described in the "Biological Activity", "Hyperproliferative Disorders", and "Binding Activity" sections below, in Example 11, 17, 18, 19, 20 and 27, and elsewhere herein. Briefly, the protein can be used for the detection, treatment, and/or prevention of Addison's Disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism), hypothalamus, and testes. The tissue distribution in testes indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that is expressed, particularly at low levels, in other tissues of the body. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:59 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1364 of SEQ ID NO:59, b is an integer of 15 to 1378, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 50

The translation product of this gene shares good protein homology with *Xenopus* NaDC-2 gene and a rabbit renal sodium/dicarboxylate cotransporter. The translation product of this gene also shares good homology with a rat placental protein which is a sodium-coupled high affinity dicarboxylate transporter. Therefore, it is likely that the translated product encoded by this gene shares similar biological activity.

This gene is expressed primarily in the placenta and colon adenocarcinoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental abnormalities as well as failure to thrive anomalies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the female reproductive system and colon, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., amniotic, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 173 as residues: Lys-166 to Gly-181. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in human placenta and the shared homology of this translation product to a rat placental protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product is produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or

survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product is produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. The tissue distribution in colon tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders involving the colon. Expression of this gene product in colon tissue indicates involvement in digestion, processing, and elimination of food, as well as a potential role for this gene as a diagnostic marker or causative agent in the development of colon cancer, and cancer in general.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:60 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1112 of SEQ ID NO:60, b is an integer of 15 to 1126, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:60, and where b is greater than or equal to a + 14.

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 51

This gene is expressed primarily in the spinal cord.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, paralysis, neurologic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of

the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken
5 from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in spinal cord indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or
10 prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease,
15 Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including
20 disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or
25 survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:61 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
5 formula of a-b, where a is any integer between 1 to 2064 of SEQ ID NO:61, b is an integer of 15 to 2078, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:61, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 52

10 This gene is expressed primarily in keratinocytes, brain, fetal tissues, pericardium, stomach, and cancerous tissues (e.g., stomach, adrenals, parathyroid, germ cell, colon, breast).

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a
15 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, skin disorders, neurodegenerative and developmental disorders, heart disease, and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above
20 tissues or cells, particularly of the cardiovascular and gastrointestinal systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, immune, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the
25 standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions.
30 Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of

Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive
5 compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation,
10 neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. The tissue distribution in keratinocytes indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment, diagnosis, and/or prevention of various skin disorders. Representative uses are described in the "Biological Activity", "Hyperproliferative Disorders", "infectious disease", and
15 "Regeneration" sections below, in Example 11, 19, and 20, and elsewhere herein. Briefly, the protein is useful in detecting, treating, and/or preventing congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's Disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's Disease, mycosis
20 fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may
25 predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, and ringworm). Moreover, the protein product of this gene may also be useful for the treatment or diagnosis of various connective tissue disorders (i.e., arthritis, trauma, tendonitis, chondromalacia and
30 inflammation, etc.), autoimmune disorders (i.e., rheumatoid arthritis, lupus, scleroderma, dermatomyositis, etc.), dwarfism, spinal deformation, joint abnormalities, and chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita,

familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). The expression within fetal tissue (e.g., spleen and liver) and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Additionally, the tissue distribution in the pericardium of the heart indicates that the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the

protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:62 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 748 of SEQ ID NO:62, b is an integer of 15 to 762, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 53

This gene is expressed primarily in the brain and in cartilage and to a lesser extent in the retina, activated T-cells, pineal gland, the lungs, and in synovial sarcoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological diseases, such as epilepsy and dementia, osteoarthritis, retinopathies, hematopoietic diseases, emphysema, and lung cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neurologic system, cartilage and musculature, vision, the hematopoietic system, and the pulmonary system expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, immune, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 176 as residues: Arg-34 to Cys-44. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain indicates polynucleotides and polypeptides
5 corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly,
10 the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive
15 compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or
20 survival. The tissue distribution in T-cells indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19,
25 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

30 Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such

as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The expression of this gene product in synovium would suggest a role in the detection and treatment of disorders and conditions afflicting the skeletal system, in particular osteoporosis, bone cancer, connective tissue disorders (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation). The protein is also useful in the diagnosis or treatment of various autoimmune disorders (i.e., rheumatoid arthritis, lupus, scleroderma, and dermatomyositis), dwarfism, spinal deformation, joint abnormalities, and chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid, etc.). Additionally, the expression within fetal tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have

applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:63 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1080 of SEQ ID NO:63, b is an integer of 15 to 1094, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 54

This gene is expressed primarily in umbilical vein endothelial cells induced by IL-4.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, angiogenesis, inflammatory disorders, hematopoietic disease.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the angiogenic and hematopoietic systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in endothelial cells indicates polynucleotides and polypeptides corresponding to this gene are useful in the detection, treatment, and/or prevention of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or embolism. For example, this gene product may represent a soluble factor produced by smooth muscle that regulates the innervation of organs or regulates the survival of neighboring neurons. Likewise, it is involved in controlling the digestive process, and such actions as peristalsis. Similarly, it is involved in controlling the vasculature in areas where smooth muscle surrounds the endothelium of blood vessels. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, and as nutritional supplements. It may also have a very wide range of biological activities. Representative uses are described in the "Chemotaxis" and "Binding Activity" sections below, in Examples 11, 12, 13, 14, 15, 16, 18, 19, and 20, and elsewhere herein. Briefly, the protein may possess the following activities: cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human

immunodeficiency virus infection, cancer, autoimmune diseases and allergy);
regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy);
stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for
treating wounds, stimulation of follicle stimulating hormone (for control of fertility);
5 chemotactic and chemokinetic activities (e.g. for treating infections, tumors);
hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction
etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's Disease); as
antimicrobials; for treating psoriasis or other hyperproliferative diseases; for
regulation of metabolism, and behavior. Also contemplated is the use of the
10 corresponding nucleic acid in gene therapy procedures.

Many polynucleotide sequences, such as EST sequences, are publicly
available and accessible through sequence databases. Some of these sequences are
related to SEQ ID NO:64 and may have been publicly available prior to conception of
the present invention. Preferably, such related polynucleotides are specifically
15 excluded from the scope of the present invention. To list every related sequence is
cumbersome. Accordingly, preferably excluded from the present invention are one or
more polynucleotides comprising a nucleotide sequence described by the general
formula of a-b, where a is any integer between 1 to 1347 of SEQ ID NO:64, b is an
integer of 15 to 1361, where both a and b correspond to the positions of nucleotide
20 residues shown in SEQ ID NO:64, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 55

This gene is expressed primarily in both normal and cancerous pancreas.

Therefore, polynucleotides and polypeptides of the invention are useful as
25 reagents for differential identification of the tissue(s) or cell type(s) present in a
biological sample and for diagnosis of diseases and conditions which include, but are
not limited to, diabetes, gastrointestinal disorders, and pancreatic cancer. Similarly,
polypeptides and antibodies directed to these polypeptides are useful in providing
immunological probes for differential identification of the tissue(s) or cell type(s). For
30 a number of disorders of the above tissues or cells, particularly of the digestive and
blood systems, expression of this gene at significantly higher or lower levels is
routinely detected in certain tissues or cell types (e.g., cancerous and wounded

tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5 The tissue distribution in pancreas indicates that the protein products of this gene are useful as a therapeutic and/or diagnostic agent for pancreatic disorders and disorders of the endocrine and exocrine system, including but not limited to diabetes, blood disorders, pancreatic cancer, gastrointestinal diseases, hormonal imbalance, autoimmune disorders, cystic fibrosis, pancreatitis, and gallstones. Furthermore, the
10 protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

15 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:65 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
20 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 933 of SEQ ID NO:65, b is an integer of 15 to 947, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where b is greater than or equal to a + 14.

25

FEATURES OF PROTEIN ENCODED BY GENE NO: 56

The translation product of this gene shares sequence homology with oxidoreductase. Preferred polypeptides of the invention comprise the following amino acid sequence: MSPLSAARAALRVYAVGAAVILAQLLRRCRGGFLEPVXPPRP
30 DRVAIVTGGTDGIGYSTANIWRDLGMHVIIAGNNSKAKQVVSKIKEETLND
KVEFLYCDLASMTSIRQFVQKFKMKKIPLHVLINNAGVMMVPQRKTRDGFEE
HFGLNYLGHFLLTNLLDTLKESGSPGHSARVVTVSSATHYVAELNMDDLQS

SACYSPHAA YAQSKLALVLFTYHLQRLLAAEGSHVTANVVDPGVVNTDXYK
HVFWATRLAKKLLGWLLFKTPDEGAWTSIYAAVTPELEGVGGRYLYNEKET
KSLHVTYNQKLQQQLWSKSCMTGVLDVTL (SEQ ID NO: 320). The mature
form of this protein begins at residue 32. Thus, polypeptides comprising residues 2-
5 330 and 32-330 of the sequence shown above are also provided. Polynucleotides
encoding such polypeptides are also provided.

A preferred polypeptide fragment of the invention comprises the following
amino acid sequence: MSPLSAARAALRVYAVGAAVILAQLLRRCRGGFLEP
VXPPRPDRVAIVTGGTDGIG YSTANIWRDLACMLS (SEQ ID NO: 321).

10 Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in breast cancer cells, osteoclastoma, wilm's
tumor, thymus stromal cells, and T cell helper I.

Therefore, polynucleotides and polypeptides of the invention are useful as
reagents for differential identification of the tissue(s) or cell type(s) present in a
15 biological sample and for diagnosis of diseases and conditions which include, but are
not limited to, cancer, e.g., breast cancer, osteoclastoma, and wilm's tumor. Similarly,
polypeptides and antibodies directed to these polypeptides are useful in providing
immunological probes for differential identification of the tissue(s) or cell type(s). For
a number of disorders of the above tissues or cells, particularly of the immune system,
20 expression of this gene at significantly higher or lower levels is routinely detected in
certain tissues or cell types (e.g., reproductive, kidney, immune, hematopoietic, and
cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, breast milk,
urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an
individual having such a disorder, relative to the standard gene expression level, i.e.,
25 the expression level in healthy tissue or bodily fluid from an individual not having the
disorder.

The tissue distribution in breast cancer tissue, combined with the homology to
oxidoreductase indicates that polynucleotides and polypeptides corresponding to this
gene are useful for diagnosis and treatment of cancer, particularly, breast cancer,
30 osteoclastoma, and wilm's tumor. This protein may play a role in the regulation of
cellular division, and may show utility in the diagnosis, treatment, and/or prevention
of developmental diseases and disorders, including cancer, and other proliferative

conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

5 Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have
10 applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue
15 differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the
20 protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

25 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:66 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
30 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1362 of SEQ ID NO:66, b is an

integer of 15 to 1376, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 57

5 This gene is expressed primarily in monocytes, T cell helper II and B cell lymphoma.

 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
10 not limited to, immune and hematopoietic diseases and/or disorders, particularly B-cell lymphoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or
15 lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not
20 having the disorder.

 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 180 as residues: Asp-30 to Val-40. Polynucleotides encoding said polypeptides are also provided.

 The tissue distribution in monocytes, T cell helper, and B cell lymphoma cells
25 indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of B cell lymphoma. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or
30 activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or

other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:67 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2420 of SEQ ID NO:67, b is an integer of 15 to 2434, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 58

This gene is expressed primarily in human lung cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, pulmonary diseases and/or disorders, particularly cancers of the lung. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., pulmonary, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, pulmonary lavage, pulmonary surfactant, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 181 as residues: Phe-39 to Asp-45. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in lung cancer tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of immune system disorders such as ARDS, cystic fibrosis, and cancer, particularly lung cancer. This protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of

potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, 5 detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in 10 proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, 15 antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:68 and may have been publicly available prior to conception of 20 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1072 of SEQ ID NO:68, b is an 25 integer of 15 to 1086, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 59

This gene is expressed primarily in larynx carcinoma and early stage human 30 lung.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental, gastrointestinal, and pulmonary diseases and/or disorders, particularly larynx carcinoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., developmental, gastrointestinal, pulmonary, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, amniotic fluid, pulmonary lavage, sputum, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 182 as residues: His-42 to Lys-49. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in larynx carcinoma and early stage human lung indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating immune system disorders such as cancer, particularly larynx carcinoma. This protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the

polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of
5 degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue
10 markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
15 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:69 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
20 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1248 of SEQ ID NO:69, b is an integer of 15 to 1262, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where b is greater than or equal to a + 14.

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 60

Preferred polypeptides of the invention comprise the following amino acid sequence: MEVTTEDTSRTDVSEPATSGGAADGVTSIAPTAVASSTTAASITTA
ASSMTVASSAPTTAASSTTVASIAPTTTASSMTAASSTPMTLALPAPTSTXTGR
TPSTTATGHPSLSTALAQVPKSSALPRTATLATLATRAQTVATTANTSSPMST
30 RPSPSKHMPSDTAASPVPPMXPQAQGPISQVSVDQPVVNTTXKSTXMPSTNTT
XEPLTQAVVDKTLVVLLLVTLFTVLVLFALQAYESYKKKDYTQVDYLI

NGMYADSEM (SEQ ID NO: 322). Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: ARCELPGLRCRPRPRAGPQAPSYCPRATRPPG ACCARMRLLEWRVYLRLTCATKDGMARECPPTWLSPPAKPDFAQRHSVK PTALQGGRWSRLGASP (SEQ ID NO: 323). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in adipocytes, osteoblasts, cerebellum, hypothalamus and Hodgkin's lymphoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic, skeletal, neural, and immune diseases and/or disorders, particularly Hodgkin's lymphoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., metabolic, skeletal, neural, immune, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 183 as residues: Pro-33 to Gln-40, Gly-51 to Arg-56. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in Hodgkin's lymphoma cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of immune system disorders such as cancer, particularly Hodgkin's lymphoma. The secreted protein can also be used to determine biological activity, to

raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, and as nutritional supplements. It may also have a very wide range of biological activities. Representative uses are described in the "Chemotaxis" and "Binding Activity" sections below, in Examples 11, 12, 13, 14, 15, 16, 18, 19, and 20, and elsewhere herein. Briefly, the protein may possess the following activities: cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's Disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:70 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1628 of SEQ ID NO:70, b is an integer of 15 to 1642, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 61

The translation product of this gene shares sequence homology with polypeptide in the cystatin family. Cystatin polypeptides are cysteine protease inhibitors. For an analysis of the composition of several members of the cystatin family see Gene (1987) 61(3):329-338, incorporated herein by reference. The cystatin activity of polypeptides encoded by this gene is measured by several assays known in the art including assays described in coowned, copending US Patent Application Serial No. 08/744,138, incorporated herein by reference. Preferred polypeptides of the invention comprise the following amino acid sequence: LPATVEFAVHTFNQQSKD
YYAYRLGHILNSWKEQVESKTVFSMELLGRTRCGKFEDDIDNCHFQESTEL
NNTFTCFFTISTRPWMTQFSLNKC (SEQ ID NO: 324). Fragments of such polypeptides having cystatin activity (cysteine protease inhibitory activity are particularly preferred). Polynucleotides encoding such polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: LLWARGLGRAKSAVPTVST MLGLPWKGGLS
WALLLLLLGSQILLIYAWHFHEQRDCDEHNVMARYLPATVEFAVHTFNQQS
KDYAYRLGHILNSWKEQVESKTVFSMELLGRTRCGKFEDDIDNCHFQ
STELNNTFTCFFTISTRPWMTQFSLNK TCLEGFH (SEQ ID NO: 325).
Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in testes and epididymus. For a review of a cystatin showing testes- specific expression see Mol. Endocrinol. (1992 Oct.) 6(10):1653-1664, incorporated herein by reference.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, They should therefore serve a protective function to regulate the activities of such endogenous proteinases, which otherwise may cause uncontrolled proteolysis and tissue damage. Cysteine proteinase activity can normally not be measured in body fluids, but can be detected extracellularly in conditions like endotoxin-induced sepsis, metastasizing cancer, and at local inflammatory processes

in rheumatoid arthritis , purulent bronchiectasis and periodontitis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, testicular, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, seminal fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 184 as residues: Phe-31 to Asp-38, Asn-59 to Tyr-65, Ser-76 to Glu-82, Thr-96 to Cys-108, Gln-111 to Asn-118. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in testes and epididymus, combined with the homology to cystatins indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that is expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product is expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent

of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Cysteine proteinase inhibitors of the cystatin superfamily are ubiquitous in the body and are generally tight-binding inhibitors of papain-like cysteine proteinases, such as cathepsins B, H, L, S, and K. They should therefore serve a protective function to regulate the activities of such endogenous proteinases, which otherwise may cause uncontrolled proteolysis and tissue damage. Cysteine proteinase activity can normally not be measured in body fluids, but can be detected extracellularly in conditions like endotoxin-induced sepsis, metastasizing cancer, and at local inflammatory processes in rheumatoid arthritis, purulent bronchiectasis and periodontitis, which indicates that a tight cystatin regulation is a necessity in the normal state. A deficiency state in which the levels of the intracellular cystatin, cystatin B, are lowered due to mutations has recently been shown to segregate with a form of progressive myoclonus epilepsy, which points to additional specialized functions of cystatins. Moreover, results showing that chicken cystatin inhibits polio virus replication, human cystatin C inhibits corona- and herpes simplex virus

replication, and human cystatin A inhibits rhabdovirus-induced apoptosis in cell cultures indicates that cystatins play additional roles in the human defense system. The cystatins constitute a superfamily of evolutionarily related proteins, all composed of at least one 100-120 residue domain with conserved sequence motifs.

5 The previously well characterized single-domain human members of this superfamily could be grouped in two protein families. The Family 1 members, cystatins (or stefins) A and B, contain approximately 100 amino acid residues, lack disulfide bridges, and are not synthesized as preproteins with signal peptides. The Family 2 cystatins (cystatins C, D, S, SN, and SA) are secreted proteins of approx.
10 120 amino acid residues (Mr 13,000-14,000) and have two characteristic intrachain disulfide bonds. Recently, we identified an additional human cystatin superfamily member by EST1 sequencing in epithelial cell derived cDNA libraries which we named cystatin E. The same cystatin was independently discovered by differential display experiments as a mRNA species down-regulated in breast tumor tissue, but
15 present in the surrounding epithelium and reported under the name cystatin M. Cystatin E/M is an atypical, secreted low-Mr cystatin in that it is a glycoprotein and just shows 30-35% sequence identity in alignments with the human Family 2 cystatins, which shows that additional cystatin families are yet to be identified. The cystatin E/M gene has been localized to chromosome 2, whereas all human Family 2
20 cystatin genes are clustered on the short arm of chromosome 20, which further stresses that cystatin E/M is just distantly related to the other secreted human low-Mr cystatins. It is believed therefore, that polypeptides encoded by this gene are useful in diagnosing and treating disease consistent with the aforementioned conditions in which cystatins are implicated.

25 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:71 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
30 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 907 of SEQ ID NO:71, b is an

integer of 15 to 921, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 62

- 5 The translation product of this gene shares sequence homology with Neutrophil Gelatinase-Associated Lipocalin which is thought to be important in immune regulation (See Genbank and Geneseq Accession Nos. embICA58127.1, and US5627034, respectively; all references and information available through these accessions are hereby incorporated herein by reference; for example, Biochem. Biophys. Res. Commun. 202 (3), 1468-1475 (1994), and FEBS Lett. 314 (3), 386-388 (1992)).

- 15 In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: LEQKLELHRGGGRSRTSGSPGLQEFGTREERGE GEQRTGREFSGNGGRAVEAARMRLLCGLWLWLSLLKVLQAQTPTPLPLPP PMQSFQGNQFQGEWFLGLAGNSFRPEHRALLNAFTATFELSDDGRFEVWN AMTRGQHCDTWSYVLIPAAQPGQFTVDHGVGRSWLLPPGTLDQFICLGRAQ GLSDDNIVFPDVTGXALDL XSLPWVAAPA (SEQ ID NO: 326). Polynucleotides
20 encoding these polypeptides are also provided.

This gene is expressed primarily in epididymus and osteoclastoma.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
25 not limited to, reproductive and skeletal diseases and/or disorders, particularly cancers such as osteoclastoma testicular cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene
30 at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, testicular, skeletal, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, seminal fluid, urine, synovial fluid and spinal fluid)

or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic
5 epitopes shown in SEQ ID NO: 185 as residues: Met-82 to Thr-90. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in epididymus and homology to neutrophil gelatinase-associated lipocalin indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of skin diseases and immune system
10 disorders such as cancer, particularly osteoclastoma. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, and as nutritional supplements. It may also have a very wide range of biological activities. Representative uses are described in the "Chemotaxis" and "Binding Activity"
15 sections below, in Examples 11, 12, 13, 14, 15, 16, 18, 19, and 20, and elsewhere herein. Briefly, the protein may possess the following activities: cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy);
20 regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction
25 etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's Disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or
30 immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:72 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
5 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 892 of SEQ ID NO:72, b is an integer of 15 to 906, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where b is greater than or equal to a + 14.

10 **FEATURES OF PROTEIN ENCODED BY GENE NO: 63**

The translation product of this gene was shown to have homology to colipase which plays an essential role in the intestinal fat digestion by anchoring lipase on lipid/water interfaces in the presence of bile salts (See Genbank Accession No. gb|AAA03513.1; all references and information available through this accession are
15 hereby incorporated by reference herein).

This gene is expressed primarily in epididymus.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
20 not limited to, reproductive diseases and/or disorders, particularly epididymus-related diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or
25 lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, seminal fluid, bile, chyme, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from
30 an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 186 as residues: Ile-40 to Cys-49, Arg-52 to Cys-57,

Ser-94 to Trp-99, Gly-105 to Gly-111. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in epididymus indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of immune system diseases and disorders of the epididymus. Polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that is expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product is expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:73 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 666 of SEQ ID NO:73, b is an integer of 15 to 680, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 64

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: MCVCKERKRGREKEGGVTPTMTSNFPFCTLILGI
5 AQAQACPGCPGDWPGLGSGVGEGLHHIRTCRTPIPCSPAPAAACLGS
ARLPCVLRLLWPVPANLSSPFRLEALHCSFWSSPLLPAHLAFFGFRDLLTDFL
LAACLLTFQKTPLELPMVAVVHLLVATPCYQMLDNLPLPSAAAN WC (SEQ ID
10 NO: 327). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in melanocytes and placenta and to a lesser extent in bone marrow and many cells of the immune system, including B-cells, dendritic cells, and T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, skin cancer and disorders of the reproductive and immune systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive and immune systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues and cell types (e.g., reproductive tissue, hematopoietic tissue, melanocytes and cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in melanocytes indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting the skin, the reproductive system, and the immune system, particularly cancers. Representative uses are described in the "Biological Activity",

"Hyperproliferative Disorders", "infectious disease", and "Regeneration" sections below, in Example 11, 19, and 20, and elsewhere herein. Briefly, the protein is useful in detecting, treating, and/or preventing congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's Disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's Disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, and ringworm). Moreover, the protein product of this gene may also be useful for the treatment or diagnosis of various connective tissue disorders (i.e., arthritis, trauma, tendonitis, chondromalacia and inflammation, etc.), autoimmune disorders (i.e., rheumatoid arthritis, lupus, scleroderma, dermatomyositis, etc.), dwarfism, spinal deformation, joint abnormalities, and chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:74 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 1619 of SEQ ID NO:74, b is an integer of 15 to 1633, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 65

Preferred polypeptides of the invention comprise the following amino acid sequence: YLWGRPRLRMRAGTSPSAPWGEEKREKLGHKLPVALQGYHPWIL
LECTVFWARVVLACFSLYLIRGPNCINRQPEPTYQKACNLDCSSDFGQER
APAWELLGPESEQRLREYTAQGLQSLASSHRWRQFKTEGKMRGGASPLPWLI
10 CFW LCSYKGSDNSLKPVVPGPTLCPQSLVSPSVHPSTRSASLGRHRAEAA
(SEQ ID NO: 328). Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the
15 following amino acid sequence: MPGILAGIPVKDLCLSLQGFRLLLCVCPGWL
SGWMGGQKGSPRIVDIG (SEQ ID NO: 329). Polynucleotides encoding these polypeptides are also provided. This gene maps to chromosome 15, accordingly, polynucleotides of the invention is used in linkage analysis as a marker for chromosome 15.

20 This gene is expressed primarily in brain and breast and to a lesser extent in the liver, pancreas, and T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
25 not limited to, disorders affecting the brain and CNS, the reproductive system, or the immune system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, the reproductive system, and the immune
30 system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., brain and other tissue of the nervous system, mammary tissue, endocrine tissue, hepatic tissue, reproductive tissue, cells

and tissue of the immune system, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 188 as residues: Met-37 to Ser-43. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting the central nervous system, the reproductive system, and the immune system, including cancers. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:75 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
5 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1008 of SEQ ID NO:75, b is an integer of 15 to 1022, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:75, and where b is greater than or equal to a + 14.

10 **FEATURES OF PROTEIN ENCODED BY GENE NO: 66**

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: AKGEERKEAFSLKMOVLSSEPISFGLMYLYLGV
15 FFHLYPGALSITTLGKHSHPPFTAEQNSTVWMEHTLFHQSPVASHLVCFQSF
AFSE (SEQ ID NO: 330). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in the brain and the immune system, in particular T-cells.

20 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders affecting the brain, such as Alzheimer's or disorders affecting the immune system, such as AIDS. Similarly, polypeptides and antibodies directed to
25 these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and CNS and the immune systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues and cell types (e.g., brain and other tissue of the nervous system, cells and
30 tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting the brain and CNS or disorders affecting the immune system. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:76 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1170 of SEQ ID NO:76, b is an

integer of 15 to 1184, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:76, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 67

5 The translation product of this gene shares sequence homology with penaeidin-2 which is thought to be a members of a new family of antimicrobial peptides from the hemolymph of shrimps *Penaeus vannamei*. The molecules display antimicrobial activity against fungi and bacteria with a predominant activity against Gram-positive bacteria.

10 In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: GPAHPASPPLMTLSLQLAELVHFVCAFQSQWT GVYPMPPLKPTPLCFA CVPCR (SEQ ID NO: 331). Polynucleotides
15 encoding these polypeptides are also provided.

 This gene is expressed primarily in spleen.

 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
20 not limited to, immune and hematopoietic diseases and/or disorders, particularly disorders affecting the spleen, including bacterial and fungal infections. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic
25 and immune systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues and cell types (e.g., immune, hematopoietic, and cells and tissue of the immune system, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard
30 gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in spleen and homology to the penaeidin family of antibiotics indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting the spleen, especially fungal and bacterial infections. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:77 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
5 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 298 of SEQ ID NO:77, b is an integer of 15 to 312, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:77, and where b is greater than or equal to a + 14.

10 **FEATURES OF PROTEIN ENCODED BY GENE NO: 68**

Contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of THP-1 cells to calcium. Thus it is likely that the product of this gene is involved in a signal
15 transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of both monocytes, in addition to other cell-lines or tissue cell types. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating immune and hematopoietic cells and tissue cell types. Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium and sodium, as well as alter pH and membrane
20 potential. Alterations in small molecule concentration can be measured to identify supernatants which bind to receptors of a particular cell.

Moreover, when tested in TF-1 cell lines, the protein product of this gene has been shown to alter the steady-state messenger RNA levels of the following genes: c-fos, c-jun, egr-1, b561, bcl-2, CD40, cyclin D2, GADPH, ICER, MAD3, p21, STAT3,
25 ID3, and STAT-1. When tested in U937 cell lines, the protein product of this gene has been shown to alter the steady-state messenger RNA levels of the following genes: egr2, MKP1, ATF3, B562, cyclin D, cyclin D2, GATA3, MAD3, p21, TGF, DHFR, and JAK3. Based upon these results, it is anticipated that polynucleotides and polypeptides corresponding to this gene are useful as agonists or antagonists of the
30 above referenced genes. Such activity is useful in therapeutic and/or diagnostic applications as referenced and more specifically discussed elsewhere herein.

In specific embodiments, polypeptides of the invention comprise the sequence: MLLEVYGDSISVTVAIPL (SEQ ID NO:332), MHSPCQSKAADGLGKSETE (SEQ ID NO: 333), and/or MLKSLGLSTN (SEQ ID NO: 334). Polynucleotides encoding these polypeptides are also provided.

5 In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: AQLAEECFYMLLEVYGDSISVTVAIPLMHSP
CQSKAADGLGKSETEMLKSLGLSTNMSPFHLLGLKVFLTWALTLAQICLY
10 FFEVQPLGLLALNFFCTATAGLKELCMHPPSLAFTPEFHTSLSPLAIPSFSGTS
VLSNSHTIPLSLYLPFPSKSRMPDTLHLLVHSLPLVHSQVLPVKDVTIEWPLC
QRCLGSTCH Q (SEQ ID NO: 335). Polynucleotides encoding these polypeptides are also provided.

The polypeptide of this gene has been determined to have a transmembrane
15 domain at about amino acid position 11 - 27 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 28 to 143 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ia membrane proteins.

20 This gene is expressed primarily in neutrophils and T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders and/or diseases affecting the immune system. Similarly,
25 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues and cell types (e.g., immune, hematopoietic, cells and tissue
30 of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 191 as residues: Pro-97 to Asp-104. Polynucleotides
5 encoding said polypeptides are also provided.

The tissue distribution in neutrophils and T-cells, combined with the detected calcium flux biological activity indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting the immune system. Representative uses are described in the "Immune
10 Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or
15 other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such
20 as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic
25 lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and
30 in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their

interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:78 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1356 of SEQ ID NO:78, b is an integer of 15 to 1370, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:78, and where b is greater than or equal to a + 14.

15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 69**

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: WIPRAAGIRHEVQVSLFQMFCFSSIFCSH
20 EHTHLPGTFWLFLFLFLILPPSCPCFLPFS LAIETVRWPCWHHPTSFELCY
PGTSIYYASRGGPXPNSEX (SEQ ID NO: 336). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as
25 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders affecting the immune system, and neutrophils in particular. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the
30 tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues and cell types (e.g., blood cells,

and cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting the immune system and neutrophils in particular. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as,

antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:79 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 354 of SEQ ID NO:79, b is an integer of 15 to 368, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:79, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 70

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: XNXKSPLTIGNKSWSTAVAAALELVDPPGCR NSARDSPELVHLGKGRPRKLMTYLCSSISLLLLKVHSSGHQDIRKAKSKVP RLLIIQCPQQRE (SEQ ID NO: 337). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in smooth muscle.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders affecting smooth muscle tissue, particularly vascular conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of smooth muscle tissue expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., muscle, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial

fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 193 as residues: Ser-18 to Val-31. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution primarily in smooth muscle indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting smooth muscle tissue. Moreover, the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:80 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1074 of SEQ ID NO:80, b is an integer of 15 to 1088, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:80, and where b is greater than or equal to a + 14.

30 FEATURES OF PROTEIN ENCODED BY GENE NO: 71

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by

the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: GPEENLSPSTPSQMPTIWVKLCLLQVCHGLFP LLKHWSQPMPLCVTLAPVSYWL (SEQ ID NO: 338). Polynucleotides encoding these polypeptides are also provided.

5 This gene is expressed primarily in fetal heart, smooth muscle, and frontal cortex.

 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, muscular, vascular, or neural diseases and/or disorders, particularly defects or injury to cardiac muscle. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., muscular, vascular, neural, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

 The tissue distribution in fetal heart indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosing and treating defects to the heart either due to injury or congenital defects. Moreover, the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Alternatively, polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection,

treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:81 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1848 of SEQ ID NO:81, b is an integer of 15 to 1862, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:81, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 72

The translation product of this gene shares sequence homology with adipose complement related protein which is thought to be important in regulating energy metabolism, insulin levels and fat stores. Moreover, the protein product of this gene has also been shown to have homology to the complement subcomponent C1q A-chain precursor and HP-25 protein (See Genbank and Geneseq Accession Nos. embICA41664.1, dbjIBAA02352.1, and W98013; all references and information

available through this accession are hereby incorporated by reference herein). Based on the sequence similarity, the translation product of this gene is expected to share at least some biological activities with complement proteins.

In another embodiment, polypeptides comprising the amino acid sequence of
5 the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: PRVRKEPEAMQWLRVRESPGEATGHRVTMG
TAALGPVWAALLLFLLMCEIPMVELTFDRAVASDCQRCCDSEDPLDPAHVSS
ASSSGRPHALPEIRPYINITILKGDKGDPGMPGLPGYMGREGPQGEPGPQGSK
10 GDKGEMGSPGAPCQKRFFAFSVGRKTALHSGEDFQTLLFERVFNLDGC
FDMATGQFAAPLRGIYFFSLNVHSWNYKETVHIMHNQKEAVILYAQPS
ERSIMQSQSVMLDLAYGDRVWVRLFKRQRENAIYSNDFDTYITFSGHLIKA
EDD (SEQ ID NO: 339). Polynucleotides encoding these polypeptides are also provided.

15 This gene is expressed primarily in placenta and, fetal kidney, and umbilical vein and to a lesser extent in fetal heart, fetal liver/spleen, microvascular endothelial cells and cancers of the lung and pharynx.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a
20 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, vascular, renal, and reproductive diseases and/or disorders, particularly cancers of the lung and pharynx. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above
25 tissues or cells, particularly of the pulmonary and immune systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., vascular, renal, reproductive, immune, hematopoietic, pulmonary, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having
30 such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 195 as residues: Asp-36 to Asp-48, Ser-57 to His-62, Lys-77 to Gly-84, Met-92 to Gly-114, Gln-203 to Ile-209, Lys-231 to Tyr-239. Polynucleotides encoding said polypeptides are also provided.

5 The tissue distribution in pharynx or lung, combined with the homology to adipose complement related proteins indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosing and treating cancers of the pharynx or lung by modifying the metabolic balance in such tissues. Moreover, the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease, 10 vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product 15 may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show 20 utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:82 and may have been publicly available prior to conception of 25 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1604 of SEQ ID NO:82, b is an 30 integer of 15 to 1618, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:82, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 73

The translation product of this gene shares sequence homology with a hypothetical 54.7 kD protein (F37A4.1) from *Caenorhabditis elegans* (SwissProt locus YPT1_CAEEL, accession P41879). The protein product of this gene also has
 5 homology to the human NG26 which is thought to contain a human major histocompatibility complex class III and is involved in T-cell maturation (See Genbank Accession No. gblAAD18079.11 (AF129756); all references and information available through this accession are hereby incorporated by reference herein; for example, J. Neurochem. 69 (6), 2516-2528 (1997)). Based on the sequence similarity,
 10 the translation product of this gene is expected to share at least some biological activities with nitric oxide synthase proteins.

Preferred polypeptides of the invention comprise the following amino acid sequence: MLYPGSVYLLQKALMPVLLQGQARLVEECNGRRAKLLACDGNE
 IDTMFVDRRGTAEPQGQKLVICCEGNAGFYEVGCVSTPLEAGYSVLGWNHP
 15 GFAGSTGVFPFQNEANAMDVVVQFAIHR LGFQPQDIIYAWSIGGFTATWAA
 MSYPDVSAMILDASFDDL VPLALKVMPDSWRGLVTRTVRQHLN LNNAEQLC
 RYQGPVLLIRRTKDEIITTTVPEDIMSNRGN DLLLKLLQHRYPRVMAEEGLRV
 VRQWLEASSQLEEASIYSRWEVEEDWCLSVLRSYQAEHGPD FFWSVGEDMS
 ADGRRQLALFLARKHLHNFEATHCTPLPAQNFQMPWHL (SEQ ID NO: 340).
 20 Polynucleotides encoding such polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: VCPKWCRFLTMLGHCCYFWQVWPASEALAA
 25 GPTPSTGSSSPSWKQHIGTSLQKTRGSLPTTTLTSGAGQSTSTGKNPAAGR
 SLEGALPAGVWPCFAQSPCTGGQQT P SSTGLRSCLVRSPATWW RTP (SEQ ID NO: 341). Polynucleotides encoding these polypeptides are also provided.

Preferred polypeptides of the invention comprise the following amino acid sequence: WIPRAAGIRHEIYREXDSERAPASVPETPTAVTAPHSSSWDTYYQ
 30 PRALEKHADSILALASVFWSISYYSSPFAFFYL YRKGYLSLSKVVPFSHYAG
 TLLLLLAGVACXRGIGRW TNPQYRQFITILEATHRNQSS ENKRQLANYNFD
 FRSWPVDFHWEPPSSRKESRGGPSRRGVALLRPEPLHRGTADTLLNRVKKL

PCQITSYLVAHTLGRRML YPGSVYLLQKALMPVLLQGQARLVEECNGRRRAK
 LLACDGNEIDTMFVDRRGTAEPQGQKL VICCEGNAGFYEVGCVSTPLEAGYS
 VLGWNHPGFAGSTGVFPQNEANAMDVVVQFAIHR LGFQPQDIIYAWSI
 GGFTATWAAMSYPDVSAMILDASFDDL VPLALKVMPDSWRGLVTRTVRQ
 5 HLNLNNAEQLCRYQGPVLLIRRTKDEIITTTVPEDIMSNRGNDLLLKLLQHR
 PRVMAEEGLRVVRQWLEASSQLEEASIYSRWEVEEDWCLSVLRSYQAEHGP
 DFPWSVGEDMSADGRRQLALFLARKHLHNFEATHCT PLPAQNFQMPWHL
 (SEQ ID NO: 342). Polynucleotides encoding these polypeptides are also provided. A
 preferred polypeptide variant of the invention comprises the following amino acid
 10 sequence: HERAXGPSRGHGELLSCVLGPRLYKIYRERDSERAPASVPETPTA
 VTAPHSSSWDTYYQP RALEKHADSILALASVFWSISYYSSPFAFFYL YRKG
 YLSLSKVVPFSHYAGTLLLLLAGV ACSEALAAGPTPSTGSSSPSWKQHIGTSLQ
 KTRGSLPTTTLTSGAGQSTSTGKNPAAGRSLEGALPAGVWPCFAQSPCTGG
 QQTPSSTGL RSCLVRSPATWWRTP (SEQ ID NO: 343). Polynucleotides
 15 encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome
 6. Accordingly, polynucleotides related to this invention are useful as a marker in
 linkage analysis for chromosome 6.

This gene is expressed primarily in cerebellum, pituitary, fetal liver, and
 20 primary dendritic cells and to a lesser extent in a wide range of tissues and
 developmental stages (i.e. fetal and adult tissue, etc.).

Therefore, polynucleotides and polypeptides of the invention are useful as
 reagents for differential identification of the tissue(s) or cell type(s) present in a
 biological sample and for diagnosis of diseases and conditions which include, but are
 25 not limited to, neural, developmental, and immune diseases and/or disorders,
 particularly those involving self recognition and T- and B-cell maturation, and cancer.
 Similarly, polypeptides and antibodies directed to these polypeptides are useful in
 providing immunological probes for differential identification of the tissue(s) or cell
 type(s). For a number of disorders of the above tissues or cells, particularly of the
 30 neural or hormonal system, expression of this gene at significantly higher or lower
 levels is routinely detected in certain tissues or cell types (e.g., neural, developmental,
 immune, hepatic, and cancerous and wounded tissues) or bodily fluids (e.g., serum,

plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 196 as residues: Thr-23 to Lys-34, Leu-41 to Ser-47, Ala-57 to Ala-68, Pro-89 to Gly-101, Pro-110 to Pro-117. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in developmental and immune cells, combined with the
10 homology to the human major histocompatibility complex class III region, indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of cancer and other proliferative disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the
15 expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

20 Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities,
25 such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that
30 influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and

in the differentiation and/or proliferation of various cell types. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to
5 isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
10 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:83 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
15 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2020 of SEQ ID NO:83, b is an integer of 15 to 2034, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:83, and where b is greater than or equal to a + 14.

20 FEATURES OF PROTEIN ENCODED BY GENE NO: 74

The translation product of this gene shares sequence homology with the br-1 protein from the snail nervous system (EMBL HPBR1 GENE) which codes for nitric oxide synthetase and which is thought to be important in mediating a variety of cellular responses, including vasodilation. Preferred polypeptides of the invention
25 comprise the following amino acid sequence: MFKRHQRLKKDSTQAEEDLSEQ
EQNQLNVLKKHGYVVGRVGRFTLYSEEQKDNIPFEFDADSLAFDMENDPVM
GTHKSTKQVELTAQDVKDAHWFYDTPGITKENCILNLLTEKEVNIVLPTQSIV
PRTFVLKPGMVLFLGAIGRIDFLQGNQSAWFTVVASNILPVHITSLDRADALY
QKHAGHTLLQIPMGGKERMAGFPPLVAEDIMLKEGLGASEAVADIKFSSAG
30 WVSVTPNFKDRLHLRGYTPEGTVLTVRPPLLPIYVNIKGQRIKKSVA YKTKKP
PSLMYNVRKKKGKINV (SEQ ID NO: 344). Polynucleotides encoding such polypeptides are also provided.

A preferred polypeptide fragment of the invention comprises the following amino acid sequence: MLPARLPFRLLSLFLRGSAPTAA RHGLREPLLERRCAA ASSFQHSSSLGRELPYDPVDTEGFGEGGDMQERFLFPEYILDPEPQPTREKQL QELQQQEEEEERQRQQRREERRQQNLARSREHPVVGHDPALPPSGVNCSS
5 GCGAXLHCQDAGVPGYLPREKFLRTAEADGGLARTVCQRCWLLSHHRRALR LQVSREQYLELVSAALRXPGPSLVLYMVDLLDLPDALLPDLPALVGPKQLIV LGNKVDLLPQDAPGYRQRLRERLWEDCARAGLLLAPGTKGHSAPSRTSHR TGRIRIRRTGPAQWSGTCG (SEQ ID NO: 345). Polynucleotides encoding these polypeptides are also provided.

10 When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is
15 a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in early stage human brain, smooth muscle,
20 and endometrial tumor and to a lesser extent in a variety of tissues representing many organs and developmental states.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
25 not limited to, cardiovascular, vascular, and neural diseases and/or disorders, particularly congestive heart disease and neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the circulatory and
30 neural systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cardiovascular, vascular, neural, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma,

urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 197 as residues: Phe-42 to Leu-48, Pro-53 to Asp-58, Pro-81 to Glu-123, Asp-256 to Trp-269, Gly-282 to Ser-306, Arg-333 to Gly-339, Arg-403 to Gln-425, Ser-446 to Asn-452, His-475 to Gln-480, Gly-592 to Met-597, Pro-635 to His-642, Lys-667 to Lys-672, Lys-678 to Ser-684. Polynucleotides
10 encoding said polypeptides are also provided.

The tissue distribution in smooth muscle and vascular tissues, combined with the homology to nitric oxide synthetase indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of congestive heart failure and neurological degenerative disorders. polynucleotides and
15 polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection,
20 treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder,
25 learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation,
30 neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to

microvascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis.

Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents
5 that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
10 related to SEQ ID NO:84 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
15 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2226 of SEQ ID NO:84, b is an integer of 15 to 2240, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:84, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 75

20 The translation product of this gene shares sequence homology with the human KE04p, in addition to an unidentified C.elegans gene.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 9 - 25 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 1 to 8
25 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type II membrane proteins.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by
30 the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: PSFRRERVETGGGGPVTHGTEGPFLPLPGGTRM NMTQARVLVAADVGLVAVLLYASIHKIEEGHLAVYYRGGALLTSPSGPGYH

IMLPFITFRSVQTTLQTDEVKNVPCGTSGGVMYIDRIE VVNMLAPYA VFDIV
RNYTADYDKTLIFNKIHHELNQFCSAHTLQEVYIELFDQIDENLKQALQKDL
NLMAPGLTIQAVRVTKPKIPEAIRRFELMEAEKTKLLIAAQKQKVVEKEA
ETERKKAVIEAEKIAQVAKIRFQQKVMKEKETEKRISEIEDAAFLAREKAKA
5 DAEYYAAHKYATSNKHKLTPYELELKKYQAIASNSKIYFGSNIPNMFVDSSC
ALKYSD IRTGRESSLPSKEALEPSGENVIQNKESTG (SEQ ID NO: 346).

Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome
10. Accordingly, polynucleotides related to this invention are useful as a marker in
10 linkage analysis for chromosome 10.

This gene is expressed primarily in fetal tissue, including 8 week whole
embryo, fetal liver spleen, nine week old early stage human, fetal heart, fetal liver,
fetal lung, and placenta and to a lesser extent in a variety of cancers, and other normal
tissues.

15 Therefore, polynucleotides and polypeptides of the invention are useful as
reagents for differential identification of the tissue(s) or cell type(s) present in a
biological sample and for diagnosis of diseases and conditions which include, but are
not limited to, cancer and diseases of fetal development. Similarly, polypeptides and
antibodies directed to these polypeptides are useful in providing immunological
20 probes for differential identification of the tissue(s) or cell type(s). For a number of
disorders of the above tissues or cells, particularly of the fetal tissues, especially the
liver, expression of this gene at significantly higher or lower levels is routinely
detected in certain tissues or cell types (e.g., developmental, hepatic, immune,
hematopoietic, pulmonary, cardiovascular, and cancerous and wounded tissues) or
25 bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another
tissue or cell sample taken from an individual having such a disorder, relative to the
standard gene expression level, i.e., the expression level in healthy tissue or bodily
fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic
30 epitopes shown in SEQ ID NO: 198 as residues: Leu-68 to Lys-74, Tyr-109 to Lys-
115, Gln-200 to Val-205, Lys-207 to Lys-214, Glu-237 to Ile-244, Ala-271 to Thr-

279, Ser-317 to Ser-329, Gln-342 to Gly-348. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution of this gene (primarily fetal tissue and cancerous tissue, both of which are undergoing rapid growth) indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of cancer and disorders of fetal development. Moreover, the expression within fetal tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as,

antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:85 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1474 of SEQ ID NO:85, b is an integer of 15 to 1488, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:85, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 76

When tested against U937 and Jurkat cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid and T-cells, and to a lesser extent in other immune cells and tissue cell types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: WSTGNASWEKKDNFILSADFEMMGLGNRR
SMKSPPLVLAALVACIIVLGFNYWIIASSRSVDLQTRIMELEGRVRRRAAERG
30 AVELKKNEFQGELEKQREQLDKIQSSHNFQLESVNKLYQDEKAVLVNNITTG
ERLIRVLQDQLKTLQRNYGRLQQDVLQFQKNQTNLERKFSYDLSQCINQMKE
VKEQCEERIEEVTKKGNEAVASRDLENNDQRQQLQALSEPQPRQLQAAGL

PHTEVPQGKGNVLGNSKSQTPAPSSEVVLDKRQVEKEETNEIQVVNEE
 PQRDRLPQEPGREQVVEDRPVGGRGFGGAGELGQTPQVQAALXVSQENPE
 MEGPERDQLVIPDGQEEEQEAAGEGRNQQKLRGEDDYNMDENEAESETDKQ
 AALAGNDRNIDVFNVE DQKRDTINLLDQREKRNHTL (SEQ ID NO: 347).

- 5 Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 9. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 9.

- 10 This gene is expressed primarily in human endometrial tumor and other tumors and to a lesser extent in a variety of other healthy adult and fetal tissues

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental diseases and/or disorders, particularly cancer and other
 15 proliferative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endometrial tissue, cervix and uterus, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues
 20 or cell types (e.g., developmental, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 25 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 199 as residues: Asn-6 to Lys-12, Leu-65 to Phe-70, Glu-73 to His-88, Gln-123 to Gln-135, Gln-142 to Leu-156, Arg-173 to Gly-181, Asp-189 to Gln-199, Ser-204 to Arg-209, Glu-219 to Gly-225, Gly-229 to Pro-238, Ser-246 to Asn-256, Glu-263 to Arg-276. Polynucleotides encoding said polypeptides
 30 are also provided.

The tissue distribution in endometrial tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of

endometrial, cervical and uterine cancer. Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

Protein, as well as, antibodies directed against the protein may show

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:86 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3160 of SEQ ID NO:86, b is an integer of 15 to 3174, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:86, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 77

The translation product of this gene shares sequence homology with protein disulfide isomerase from *Acanthamoeba castellanii* (See Genbank Locus ACADISPROA accession L28174, genpep locus 456013) which is thought to be important in converting proteins into their native conformations. The protein product of this gene was also shown to have homology to a phospholipase C homologue

derived from a mast cell cDNA library (See Geneseq Accession No. R99411). All references and information available through these accessions are hereby incorporated by reference herein - for example, Gene 150 (1), 175-179 (1994).

Included in this invention as preferred domains are endoplasmic reticulum
 5 targeting sequence domain and the thioredoxin family active site domain, which were identified using the ProSite analysis tool (Swiss Institute of Bioinformatics). Proteins that permanently reside in the lumen of the endoplasmic reticulum (ER) seem to be distinguished from newly synthesized secretory proteins by the presence of the C-terminal sequence Lys-Asp-Glu-Leu (KDEL) [1,2]. While KDEL is the preferred
 10 signal in many species, variants of that signal are used by different species. This situation is described in the following table.

Signal	Species-----
15 KDEL	Vertebrates, Drosophila, Caenorhabditis elegans, plants
HDEL	Saccharomyces cerevisiae, Kluyveromyces lactis, plants
DDEL	Kluyveromyces lactis
ADEL	Schizosaccharomyces pombe (fission yeast)
20 SDEL	Plasmodium falciparum

The signal is usually very strictly conserved in major ER proteins but some minor ER proteins have divergent sequences (probably because efficient retention of these proteins is not crucial to the cell). Proteins bearing the KDEL-type signal are not simply held in the ER, but are selectively retrieved from a post-ER compartment by a
 25 receptor and returned to their normal location. The consensus pattern is as follows: [KRHQSA]-[DENQ]-E-L>. Thioredoxins are small proteins of approximately one hundred amino- acid residues which participate in various redox reactions via the reversible oxidation of an active center disulfide bond. They exist in either a reduced form or an oxidized form where the two cysteine residues are linked in an
 30 intramolecular disulfide bond. Thioredoxin is present in prokaryotes and eukaryotes and the sequence around the redox-active disulfide bond is well conserved. Bacteriophage T4 also encodes for a thioredoxin but its primary structure is not homologous to bacterial, plant and vertebrate thioredoxins. A number of eukaryotic

proteins contain domains evolutionary related to thioredoxin, all of them seem to be protein disulphide isomerases (PDI). PDI (EC 5.3.4.1) is an endoplasmic reticulum enzyme that catalyzes the rearrangement of disulfide bonds in various proteins. The various forms of PDI which are currently known are: - PDI major isozyme; a
5 multifunctional protein that also function as the beta subunit of prolyl 4-hydroxylase (EC 1.14.11.2), as a component of oligosaccharyl transferase (EC 2.4.1.119), as thyroxine deiodinase (EC 3.8. 1.4), as glutathione-insulin transhydrogenase (EC 1.8.4.2) and as a thyroid hormone-binding protein - ERp60 (ER-60; 58 Kd microsomal protein). ERp60 was originally thought to be a phosphoinositide-specific
10 phospholipase C isozyme and later to be a protease. - ERp72. - P5. All PDI contains two or three (ERp72) copies of the thioredoxin domain. The consensus pattern is as follows: [LIVMF]-[LIVMSTA]-x-[LIVMFYC]-[FYWSTHE]-x(2)-[FYWGNT]-C-[GATPLVE]-[PHYWSTA]-C-x(6)-[LIVMFYWT]. The two C's form the redox-active bond.

15 Preferred polypeptides of the invention comprise the following amino acid sequence: SLHRFVLSQAKDEL (SEQ ID NO: 348), FIKFFAPWCGHCKALAPTW (SEQ ID NO: 349), and/or FIKFYAPWCGHCKTLAPTW (SEQ ID NO: 350). Polynucleotides encoding these polypeptides are also provided.

Further preferred are polypeptides comprising the endoplasmic reticulum
20 targeting sequence domain and thioredoxin family active site domain of the sequence referenced in Table for this gene, and at least 5, 10, 15, 20, 25, 30, 50, or 75 additional contiguous amino acid residues of this referenced sequence. The additional contiguous amino acid residues is N-terminal or C- terminal to the endoplasmic reticulum targeting sequence domain and thioredoxin family active site domain.
25 Alternatively, the additional contiguous amino acid residues is both N-terminal and C-terminal to the endoplasmic reticulum targeting sequence domain and thioredoxin family active site domain, wherein the total N- and C-terminal contiguous amino acid residues equal the specified number. Based on the sequence similarity, the translation product of this gene is expected to share at least some biological activities with
30 thioredoxin proteins. Such activities are known in the art, some of which are described elsewhere herein.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: RRGRGVPGPRGRRRLWSAACGHCQRLQPTWN
5 DLGDKYNSMEXAKVYVAKVDCTAHSDVCSAQGVRGYPTLKLFPKGQEA
KYQGPRDFQTLLENWMLQTLNEEPVTPEPEVEPPSAPELKQGLYELSASNFEH
VAQGDHFIKFFAPWCGHCKALAPTWEQLALGLEHSETVKIGKVDCTQHY
ELCSGNQVRGYPTLLWFRDGKKVDQYKGKRDLESLREYVESQLQRTETGA
TETVTPSEAPVLAAEPEADKGTVLALTENNFDITIAEGITFIKFYAPWCGHC
10 KTLAPTWEELSKKEFPGLAGVKIAEVDCTAERNICSKYSVRGYPTLLLFRGGK
KVSEHSGGRDLDS LHRFVLSQAKDEL (SEQ ID NO: 351). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in human chondrosarcoma and endothelial cells and to a lesser extent in a wide range of normal and diseased adult and fetal
15 tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, chondrosarcoma and other cancers and proliferative disorders.
20 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., vascular, skeletal,
25 developmental, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30 The tissue distribution in chondrosarcoma, combined with the homology to protein disulfide isomerase and phospholipase C indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of

chondrosarcoma and other cancers and proliferative disorders, and possibly as a reagent for in vitro production of proteins. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation
5 and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of
10 potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types
15 of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new
20 insight into the regulation of cellular growth and proliferation. Moreover, the expression in endothelial cells indicates the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis,
25 and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed
30 tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:87 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
5 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2766 of SEQ ID NO:87, b is an integer of 15 to 2780, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:87, and where b is greater than or equal to a + 14.

10 **FEATURES OF PROTEIN ENCODED BY GENE NO: 78**

This gene is expressed primarily in thyroid and thymus

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
15 not limited to, thyroid diseases including thyroid cancer and diseases of function including Grave's Disease, hyper- and hypo- thyroidism as well as Diseases of the thymus. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,
20 particularly of the endocrine and immune systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., endocrine, immune, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene
25 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in thyroid cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of diseases of the thyroid and thymus. Representative uses are
30 described in the "Biological Activity", "Hyperproliferative Disorders", and "Binding Activity" sections below, in Example 11, 17, 18, 19, 20 and 27, and elsewhere herein. Briefly, the protein can be used for the detection, treatment, and/or prevention of

Addison's Disease, Cushing's Syndrome, and disorders and/or cancers of the pancrease (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism), hypothallamus, and testes. Furthermore, the protein may also
5 be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

10 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:88 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
15 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1047 of SEQ ID NO:88, b is an integer of 15 to 1061, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:88, and where b is greater than or equal to a + 14.

20

FEATURES OF PROTEIN ENCODED BY GENE NO: 79

The translation product of this gene shares sequence homology with collagen which is thought to be important as a structural material in a variety of human tissues and products including hair, nails, muscle and bone.

25 A preferred polypeptide fragment of the invention comprises the following amino acid sequence: MRPQGPAASPQRLRGLLLLLLLQLPAPSSASEIPKGKQK AHSGRGRWWTCIMECAYKGQQECLVETGALGPMAFRVHLGSQVGMDSKEK RGNV (SEQ ID NO: 352). Polynucleotides encoding these polypeptides are also provided.

30 This gene is expressed primarily in smooth muscle and to a lesser extent in 12 week old early stage human, epididymus, healing groin wound, synovial hypoxia,

stromal cells, ulcerative colitis, breast and 8 week old embryo, as well as a variety of other normal and diseased cell types from adult and fetal tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer and other proliferative disorders as well as Diseases of smooth muscle. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the muscular system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., vascular, developmental, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 202 as residues: Glu-32 to Glu-46, Pro-63 to Ala-71, Pro-81 to Lys-90, Ser-97 to Trp-111, Lys-130 to Ser-135, Leu-147 to Cys-154, Asp-179 to Asn-186, Ser-219 to Gly-229. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in smooth muscle and homology to collagen indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of diseases of vascular diseases and/or disorders. Representative uses are described in the "Biological Activity", "Hyperproliferative Disorders", "infectious disease", and "Regeneration" sections below, in Example 11, 19, and 20, and elsewhere herein. Briefly, the protein is useful in detecting, treating, and/or preventing congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's Disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's Disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis),

atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial
5 infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athletes foot, and ringworm).

Moreover, the protein product of this gene may also be useful for the treatment or diagnosis of various connective tissue disorders (i.e., arthritis, trauma,
10 tendonitis, chondromalacia and inflammation, etc.), autoimmune disorders (i.e., rheumatoid arthritis, lupus, scleroderma, dermatomyositis, etc.), dwarfism, spinal deformation, joint abnormalities, and chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Moreover, the protein is useful in the detection,
15 treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or
20 receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
25 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:89 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
30 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1328 of SEQ ID NO:89, b is an

integer of 15 to 1342, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:89, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 80

5 This gene is expressed primarily in immune cells and to a lesser extent in a wide variety of human tissues.

 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
10 not limited to, T cell or B cell leukemia and various immunodeficiencies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in
15 certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 203 as residues: Gly-3 to Gln-9. Polynucleotides encoding said polypeptides are also provided.

 The tissue distribution in immune cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of
25 immune system diseases such as immunodeficiencies and T cell and/or B cell leukemia. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell
30 lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory
5 bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's
10 Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the
15 protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:90 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
25 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 756 of SEQ ID NO:90, b is an integer of 15 to 770, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:90, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 81

The translation product of this gene shares sequence homology with IgE receptor. See for example, Isolation and Characterization of cDNAs coding for the Beta Subunit of the High-affinity Receptor for Immunoglobulin E, Proc. Natl. Acad. Sci. U S A. (1988 Sep.) 85(17): 6483-6487. Based on the sequence similarity, the translation product of this gene is expected to share at least some biological activities with IgE receptor proteins. Such activities are known in the art, some of which are described elsewhere herein. IgE and its receptors are believed to have evolved as a mechanism to protect mammals against parasites. But other and intrinsically innocuous antigens can subvert this system to provoke an allergic response. For human populations in industrialized countries, allergy and asthma now represent a far greater threat than parasitic infection, and the main impetus for current studies of the IgE system is the hope of understanding and intervening in the aetiology of allergic diseases. The high-affinity receptor for immunoglobulin (Ig) E (Fc epsilon RI) on mast cells and basophils plays a key role in IgE-mediated allergies. Fc epsilon RI is composed of one alpha, one beta, and two gamma chains, which are all required for cell surface expression of Fc epsilon RI, but only the alpha chain is involved in the binding to IgE. Fc epsilon RI-IgE interaction is highly species specific, and rodent Fc epsilon RI does not bind human IgE. New homolog can be used to develop anti-allergic agents. FcR deliver signals when they are aggregated at the cell surface. The aggregation of FcR having immunoreceptor tyrosine-based activation motifs (ITAMs) activates sequentially src family tyrosine kinases and syk family tyrosine kinases that connect transduced signals to common activation pathways shared with other receptors. FcR with ITAMs elicit cell activation, endocytosis, and phagocytosis. The nature of responses depends primarily on the cell type. The aggregation of FcR without ITAM does not trigger cell activation. Most of these FcR internalize their ligands, which can be endocytosed, phagocytosed, or transcytosed. The fate of internalized receptor-ligand complexes depends on defined sequences in the intracytoplasmic domain of the receptors. The coaggregation of different FcR results in positive or negative cooperation. Some FcR without ITAM use FcR with ITAM as signal transduction subunits. The coaggregation of antigen receptors or of FcR having ITAMs with FcR having immunoreceptor tyrosine-based inhibition motifs (ITIMs)

negatively regulates cell activation. FcR therefore appear as the subunits of multichain receptors whose constitution is not predetermined and which deliver adaptative messages as a function of the environment.

The polypeptide of this gene has been determined to have four transmembrane
5 domains at about amino acid position 51 - 67, 89 - 105, 119 - 135, and 190 - 206 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type IIIa membrane proteins.

In another embodiment, polypeptides comprising the amino acid sequence of
10 the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: ETRVKTSLELLRTQLEPTGTVGNTIMTSQPVPN ETIIVLPSNVINFSQAEKPEPTNQGQDSLKKHLHAEIKVIGTIQILCGMMVLSL GILASASFSPNFTQVTSTLLNSAYFIGPFFFIISGSLSIATEKRLTKLLVHSSLV
15 GSILSALSALVGFIILSVKQATLNPASLQCELDKNNIPTRSYVSYFYHDSLYTT DCYTAKASLAGXLSLMLICTLLEFCLAVLTAVLRWKQAYSDFPGSVLFLPH SYIGNSGMSSKMTHDCGYEELLTS (SEQ ID NO: 353). Polynucleotides encoding these polypeptides are also provided.

A preferred polypeptide fragment of the invention comprises the following
20 amino acid sequence: MMVLSLGIILASASFSPNFTQVTSTLLNSAYFIGPFFFI ISGSLSIATEKRLTKLLVHSSLVGSILSALSALVGFIILSVKQATLNPASLQC ELDKNNIPTRSYVSYFYHDSLYTTDCYTAKASLAGXLSLMLICTLLEFCL AVLTAVLRWKQAYSDFPGSVLFLPHSYIGNSGMSSKMTHDCGYEELLTS (SEQ ID NO: 354). Polynucleotides encoding these polypeptides are also provided.

25 The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in immune system tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as
30 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune system diseases and/or disorders such as cancer. Similarly,

polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in
5 certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 204 as residues: Gln-23 to Lys-39, Glu-150 to Thr-158. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in immune cells and tissues combined with the homology to IgE receptor indicates that polynucleotides and polypeptides
15 corresponding to this gene are useful for diagnosis and treatment of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell
20 lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for
25 immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity
30 disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that

influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:91 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1556 of SEQ ID NO:91, b is an integer of 15 to 1570, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:91, and where b is greater than or equal to a + 14.

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 82

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: GASCEGGGAAARAALGVHRSQKALLVFRRTL
 30 SNLLYMPLLRGLLWLQVLCAGPLHTEAVVLLVPSDDGRAFLRSRLHPEAH
 VPPAADRGASLQCVLHQAAPKSRPRSPAAGAALLHXPRRTGDEPCREFHGN
 GFFPGPTQLTPGECGLPAPSSLLQHASAPVRTGSEGQVVGCPRARGETGEGLSL

AFLSSLMFTSRNGLVGC GASCEGGGAAARAALGVHRSQKALLVFRRTL
LYMPLLRGLLWLQVLCAGPLHTEAVVLLVPSDDGRAFLRSRLHPEAHVPP
AAD RGASLQCVLHQAAPKSRPRSPAAGAALLHXPRRTGDEPCREFHGNGFP
GPTQLTPGECGLPAPSSLLQHASAPVRTGSEGQVVGCPRARGETGEGLSLA
5 FLSSLMFTSRNGLVGC (SEQ ID NO: 355). Polynucleotides encoding these
polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome
7. Accordingly, polynucleotides related to this invention are useful as a marker in
linkage analysis for chromosome 7.

10 This gene is expressed primarily in activated T cells, and to a lesser extent in a
wide variety of human tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as
reagents for differential identification of the tissue(s) or cell type(s) present in a
biological sample and for diagnosis of diseases and conditions which include, but are
15 not limited to, immune and hematopoietic diseases and/or disorders, particularly
immunodeficiencies. Similarly, polypeptides and antibodies directed to these
polypeptides are useful in providing immunological probes for differential
identification of the tissue(s) or cell type(s). For a number of disorders of the above
tissues or cells, particularly of the immune system, expression of this gene at
20 significantly higher or lower levels is routinely detected in certain tissues or cell types
(e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids
(e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell
sample taken from an individual having such a disorder, relative to the standard gene
expression level, i.e., the expression level in healthy tissue or bodily fluid from an
25 individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic
epitopes shown in SEQ ID NO: 205 as residues: Pro-67 to Ser-73. Polynucleotides
encoding said polypeptides are also provided.

The tissue distribution in activated T cells indicates that polynucleotides and
30 polypeptides corresponding to this gene are useful for diagnosis and treatment of
immunodeficiencies. Representative uses are described in the "Immune Activity" and
"infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and

elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes
5 suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such
10 as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic
15 lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and
20 in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or
25 immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:92 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
30 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 2936 of SEQ ID NO:92, b is an integer of 15 to 2950, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:92, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 83

The translation product of this gene was shown to have homology to the human transmembrane protein (See Genbank Accession No. gblAAC51364.11 (AF000959); all references and information available through this accession are hereby incorporated by reference herein; for example, Genomics 42 (2), 245-251
10 (1997)) which is thought to be implicated in velo-cardio-facial syndrome.

A preferred polypeptide fragment of the invention comprises the following amino acid sequence: MGSAALEILGLVLCLVGWGGILACGLPMWQVTAFLD
HNIVTAQTTWKGLWMSCVVQSTGTCSAKCTTRCWL (SEQ ID NO: 356).

Polynucleotides encoding these polypeptides are also provided.

15 The gene encoding the disclosed cDNA is believed to reside on chromosome 22. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 22.

This gene is expressed primarily in dementia brain tissue, and to a lesser extent in a wide variety of human tissues.

20 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural diseases and/or disorders, particularly dementia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing
25 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or
30 another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 206 as residues: Ser-201 to Tyr-217. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in dementia brain tissue, combined with the homology
5 to the transmembrane protein indicates that polynucleotides and polypeptides
corresponding to this gene are useful for diagnosis and treatment of dementia, and
potentially for velo-cardio-facial syndrome. Representative uses are described in the
"Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11,
15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the
10 detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease,
Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating
diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal
cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia,
mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder,
15 learning disabilities, ALS, psychoses, autism, and altered behaviors, including
disorders in feeding, sleep patterns, balance, and perception. In addition, elevated
expression of this gene product in regions of the brain indicates it plays a role in
normal neural function.

Potentially, this gene product is involved in synapse formation,
20 neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or
survival. Furthermore, the protein may also be used to determine biological activity,
to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to
identify agents that modulate their interactions, in addition to its use as a nutritional
supplement. Protein, as well as, antibodies directed against the protein may show
25 utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
available and accessible through sequence databases. Some of these sequences are
related to SEQ ID NO:93 and may have been publicly available prior to conception of
the present invention. Preferably, such related polynucleotides are specifically
30 excluded from the scope of the present invention. To list every related sequence is
cumbersome. Accordingly, preferably excluded from the present invention are one or
more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 1708 of SEQ ID NO:93, b is an integer of 15 to 1722, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:93, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 84

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: LKRAPPGPALAKGLLQPSSTFQALETNIGDQVR
10 RHSTAVVIREMTSYILISFVLLIGVGCIEKDQSCPVFGGRKRLHLLFVGGQLRQ
VRMLRGELSCACYRPHVQALQLGGCTCF (SEQ ID NO: 357). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in the adult pulmonary system.

Therefore, polynucleotides and polypeptides of the invention are useful as
15 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cystic fibrosis, bronchitis and any pulmonary disorders in general. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell
20 type(s). For a number of disorders of the above tissues or cells, particularly of the pulmonary system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., pulmonary, cardiovascular, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, pulmonary surfactant, pulmonary lavage/sputum, synovial fluid and spinal fluid) or
25 another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution of this gene only in the pulmonary system indicates that it plays a key role in the functioning of the pulmonary system. This would suggest
30 that misregulation of the expression of this protein product in the adult could lead to lymphoma or sarcoma formation, particularly in the lung and the protein product could be used either in the treatment and/or detection of these disease states. The gene

or gene product may also useful in the treatment and/or detection of pulmonary defects such as pulmonary edema and embolism, bronchitis and cystic fibrosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:94 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 621 of SEQ ID NO:94, b is an integer of 15 to 635, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:94, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 85

The translation product of this gene was found to be homologous to CAM proteins. Based on the sequence similarity, the translation product of this gene is expected to share at least some biological activities with CAM proteins. Such activities are known in the art, some of which are described elsewhere herein.

A preferred polypeptide variant of the invention comprises the following amino acid sequence: MLCPWRTANLGLLLILTIFLVAEAEGAAQPNNSLM LQTSKENHALASSSLCMDEKQITQNYSKVLAEVNTSWPVKMATNAVLC CPPIALRNLIITWEILRGQPSCTKAYKKETNETKETNCTDERITWVSRPDQ NSDLQIRTVAITHDGYRCIMVTPDGNFHRGYHLQVLVTPEVTLFQNRNRTA VCKAVAGKPAAHISWIPEGDCATKQEYWSNGTVTVKSTCHWEVHNVSTV NCHVSHLTGNKSLYIELLPVPGAKKSSKLYIPYIILTIILTIVGXIWLLKVNG CXKYKLNKPESTPVVEEDEMOPYAFYTEKNNPLXXTTNKVKASEALQSEV

DTDLHTL (SEQ ID NO:208). Polynucleotides encoding these polypeptides are also provided.

5 The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 271 - 287 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 288 to 348 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ia membrane proteins.

This gene is expressed primarily in dendritic cells.

10 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunodeficiency, tumor necrosis, infection, lymphomas, auto-immunities, cancer, metastasis, wound healing, inflammation, anemias
15 (leukemia) and other hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell
20 types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 208 as residues: Asp-53 to Tyr-61, Pro-105 to Ile-128, Arg-133 to Leu-140, Gln-182 to Ala-188, Pro-205 to Asn-218, Gly-259 to Ala-264, Asn-290 to Ser-302, Glu-307 to Tyr-314, Tyr-317 to Lys-332. Polynucleotides encoding said polypeptides are also provided.

30 The tissue distribution in dendritic cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of immune disorders including: leukemias, lymphomas, auto-immunities,

immunodeficiencies (e.g. AIDS), immuno-suppressive conditions (transplantation) and hematopoietic disorders. In addition this gene product is applicable in conditions of general microbial infection, inflammation or cancer. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in

5 Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the

10 treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory

15 bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's

20 Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the

25 protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:95 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
5 formula of a-b, where a is any integer between 1 to 3784 of SEQ ID NO:95, b is an integer of 15 to 3798, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:95, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 86

10 In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: VIKLICPAAFPVYFQDMARGCVCSLCASVCIFLS
SLFPLLPSVHSVNIISCLLLSKCFEGLELMCEHL YQLSQLHVLHHIFS YLLCTP
15 (SEQ ID NO: 358). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in embryonic tissue and to a lesser extent in in a variety of other tissues and cell types.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a
20 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental anomalies, fetal deficiencies, cancer and neoplastic states. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the
25 developing fetus, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., developmental, differentiating, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression
30 level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in embryonic tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of developmental anomalies, fetal deficiencies and pre-natal disorders, as well as abnormal cell proliferation and/or differentiation, neoplastic states and cancer.

5 Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders"

10 and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent

15 of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the

20 polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in

25 modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their

30 interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:96 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
5 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2669 of SEQ ID NO:96, b is an integer of 15 to 2683, where both a and b correspond to the positions of nucleotide
10 residues shown in SEQ ID NO:96, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 87

The translation product of this gene shares sequence homology with inter-alpha-trypsin inhibitor which is thought to be important in inhibition of trypsin and
15 other serine proteases (See Genbank Accession No. pirlS30350IS30350; all references and information available through this accession are hereby incorporated herein by reference; for example, Eur. J. Biochem. 179 (1), 147-154 (1989), J. Biol. Chem. 264 (27), 15975-15981 (1989), and J. Biol. Chem. 266 (2), 747-751 (1991)).

Contact of cells with supernatant expressing the product of this gene has been
20 shown to increase the permeability of the plasma membrane of THP-1 cells to calcium. Thus it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of both monocytes, in addition to other cell-lines or tissue cell types. Thus, polynucleotides and polypeptides have uses which include, but are
25 not limited to, activating monocytes, and to a lesser extent, other immune and/or hematopoietic cells. Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium and sodium, as well as alter pH and membrane potential. Alterations in small molecule concentration can be measured to identify supernatants which bind to receptors of a particular cell.

30 In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the

following amino acid sequence: YXIPGSTHASGRQGRGSGREDDSGPPPSTVINQ
NETFANIIFKPTVVQQARIAQNGILGDFIIRYDVNREQSIGDIQVLNGYFVHYF
APKDLPLPKNVVFLDSSASMVGTKLRQTKDALFTILHDLRPQDRFSIIGFS
NRIKVKDHLISVTPDSIRDGKVYIHHMSPTGGTDINGVLQRAIRLLNKYVAH
5 SGIGDRSVSLIVFLTDG KPTVGETHTLKILNNTREAARGQVCIFTIGINDVD
FRLLEKLSLENCGLTRRVHEEEDAGSQLIGFYDEIRTPLLSDIRIDYPPSSVVQ
ATKTLFPNYFNGSEIIIAGKLVDRKLDHLHVEVTASNSKKFIIKTDVPVRPQK
AGKDVGTGSPRPGDGEGDXNHIERLWSYLTTKELLSSWLQSDDEPEKERLRQ
RAQALAVSYRFLTPTFTSMKL RGPVPRMDGLEEAHGMSAAMGPEPVVQSVR
10 GAGTQPGPLLKKPYQPRIKISKTSVDGDPHFV VDFPLSRLTVCFNIDGQPGDIL
RLVSDHRDSGVTVNGELIGAPAPPNGHKKQRTYLRTITILINKPERSYLEITPS
RVILDGGDRLVLPCNQSVVVGSGWGLEVSVSANANVTVTIQGSIAFVILHLYK
KPAFQRHHLGFYIANSEGLSSNCHGLLGQFLNQDARLTEDPAGPSQNLTHP
LLLQVGEGPEAVLTVKGHQVPVVKQRKIYN GEEQXDCWFARNMPPN
15 (SEQ ID NO: 359). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in placenta and adipose tissue and to a lesser extent in several other organs and tissues including cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a
20 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of developing organs and metabolic diseases, in addition to vascular diseases and conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above
25 tissues or cells, particularly of the developing systems and metabolic systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative
30 to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 210 as residues: Lys-5 to Lys-10, Asn-33 to Lys-39, Asp-48 to Lys-54, Pro-62 to Asp-67, Asn-116 to Arg-123, His-157 to Ala-162, Val-242 to Lys-249, Val-251 to Asp-264. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in placenta, combined with the homology to inter-alpha-trypsin inhibitor and the detected calcium flux biological activity indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of disorders of developing and metabolic systems. This protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Moreover, the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease,

vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Polynucleotides and polypeptides of the invention are also useful for the treatment, detection, and/or prevention of inflammation, tumor invasion and metastasis, wound healing, liver disease, disseminated intravascular coagulation, alzheimer's Disease, ophthalmic disease, apoptosis, tissue remodeling, intrauterine growth retardation, preeclampsia, angiogenesis, cell migration, fetal development, trophoblast implantation, ovulation, pemphigus and psoriasis, and antiviral therapy. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:97 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2167 of SEQ ID NO:97, b is an integer of 15 to 2181, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:97, and where b is greater than or equal to a + 14.

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 88

The translation product of this gene was shown to have homology to the human colon carcinoma antigen NY-CO-7 (See Genbank and Geneseq Accession Nos. gblAAC18038.11 (AF039689) and WO9904265; all references available through this accession are hereby incorporated herein by reference; for example, Int. J. Cancer 76 (5), 652-658 (1998)).

This gene is expressed primarily in breast and breast cancer and to a lesser extent in several other organs and tissues including cancers.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of reproductive organs and the gastrointestinal system, including cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., gastrointestinal, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, breast milk, chyme, bile, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 211 as residues: Gly-22 to Gly-28, Leu-71 to Phe-77, Asn-101 to Val-108, Pro-122 to Ser-127, Arg-149 to Pro-154, Gly-191 to Phe-196, Pro-199 to Thr-211. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in breast and breast cancer tissue, combined with the homology to a colon cancer antigen indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of disorders of the reproductive systems and cancers. This protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of

potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:98 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1943 of SEQ ID NO:98, b is an integer of 15 to 1957, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:98, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 89

The translation product of this gene shares sequence homology with the amino acid and protein sequence of a *Xenopus* transmembrane protein of unknown function. The very 5'-end of the contig is identical to the mRNA for the human LGN mosaic protein. Based on the sequence similarity, the translation product of this gene is

expected to share at least some biological activities with LGN mosaic proteins. Such activities are known in the art, some of which are described elsewhere herein.

Preferred polypeptides of the invention comprise the following amino acid sequence:

PRVRPPTKALAVTFTTFVTEPLKHIGKGTGEFIKALMKEIPALLHLPVLIIMAL
5 AILSFCYGAGKSVHVLRHIGGPEREPPQALRPRDRRRQEEIDYRPDGGAGDAD
FHYRGQMGPTEQGPYAKTYEGRREILRERDVDLRFQTGNKSPEVLRAFDVPD
AEAREHPTVVPSHKSPVLDTKPKETGGILGEGTPKESSTESSQSAKPVSGQDTS
GNTEGSPA AEKAQLKSEAAGSPDQGSTYSPARGVAGPRGQDPVSSPCG (SEQ
ID NO:339). Polynucleotides encoding such polypeptides are also provided.

10 The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in small intestine and adipocytes and to a lesser extent in various other normal and transformed cell types, mostly of endocrine
15 origin.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, conditions of growth and metabolism. Similarly, polypeptides and
20 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive and endocrine systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., metabolic, gastrointestinal, and
25 cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, bile, chyme, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 212 as residues: Pro-40 to Gly-68, Gly-79 to Arg-93, Phe-106 to Glu-114, Pro-122 to His-129, Thr-143 to Gly-149, Gly-155 to Ala-168,

Val-171 to Gly-182, Ala-195 to Pro-207, Pro-214 to Val-220. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in small intestine indicates that polynucleotides and polypeptides corresponding to this gene are useful for study and treatment of disorders of growth and metabolism as well as endocrine abnormalities. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:99 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1098 of SEQ ID NO:99, b is an integer of 15 to 1112, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:99, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 90

The translation product of this gene shares sequence homology with IgE receptor beta chain which is thought to be important in immune function.

This gene is expressed primarily in kidney medulla tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and renal diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and renal systems,

expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, renal, urogenital, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such
5 a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in kidney renal medulla tissue, combined with the homology to the IgE receptor beta chain indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment of immune and
10 renal disorders. The protein product of this gene could be used in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe
15 kidney, polycystic kidney, and Falconi's syndrome. Alternatively, this gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene
20 product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and
25 tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits
30 hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the

protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:100 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 873 of SEQ ID NO:100, b is an integer of 15 to 887, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:100, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 91

The translation product of this gene shares sequence homology with Diff 40 gene product (See Genbank Accession No. gblAAC51134.1; all references and information available through this reference are hereby incorporated herein).

Preferred polypeptides of the invention comprise the following amino acid sequence: PRVRSIKVTELKGLANHVVVGSVSCETKDLFAALPQVVAVDIN
DLGTIKLSLEVTWSPFDKDDQPSAASSVNKASTVTKRFSTYSQSPDTPS
LREQAFYNMLRRQEELNGTAWLSSESSDDSSSPQLSGTARHSPAPRPLV
25 QQPEPLPIQVAFRRPETPSSGPLDEEGAVAPVLANGHAPYSRTLHISEASVNA
ALAEASVEAVGPKSLSWGSPPTHAPATHGKHPSVPPALDPGHSATSST
LGTGTSVPTSTDPAPSAHLDSVHKSTDSGPSELPGPHTTTTGSTYSAITTTTHS
APSPLTHTTTGSTHKPIISTLTGPTLNIIGPVQTTTSPHTMPSPSSHNSNPQ
YVDFCSSVCDNIFVHYVIGIFFHTLYSSKTL (SEQ ID NO:360), and/or PRVRS
30 IKVTELKGLANHVVVGSVSCETKDLFAALPQVVAVDINDLGTIKLSLEVTWSP
FDKDDQPSAASSVNKASTVTKRFSTYSQSPDTPSLREQAFYNMLRRQEEL
NGTAWLSSESSDDSSSPQLSGTARHSPAP RPLVQQPEPLPIQVAFRRPET

PSSGPLDEEGAVAPVLANGHAPYSRTLSEASVNAALAEASVEAVGPKSL
SWGPSPPTHPAPTHGKHPSPVPPALDPGHSATSSTLGTTGTVPTSTD (SEQ ID
NO: 361). Polynucleotides encoding these polypeptides are also provided.

Polypeptides of the invention do not consist of the primary amino acid sequence
5 shown as Geneseq Accession No.W69430, which is hereby incorporated herein by
reference.

This gene is expressed primarily in liver and to a lesser extent in gall bladder
tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as
10 reagents for differential identification of the tissue(s) or cell type(s) present in a
biological sample and for diagnosis of diseases and conditions which include, but are
not limited to, metabolic and endocrine diseases and/or disorders, particularly hepatic
and gall bladder disorders. Similarly, polypeptides and antibodies directed to these
polypeptides are useful in providing immunological probes for differential
15 identification of the tissue(s) or cell type(s). For a number of disorders of the above
tissues or cells, particularly of the metabolic and endocrine systems, expression of this
gene at significantly higher or lower levels is routinely detected in certain tissues or
cell types (e.g., hepatic, metabolic, gall bladder, gastrointestinal, and cancerous and
wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, bile, synovial
20 fluid and spinal fluid) or another tissue or cell sample taken from an individual having
such a disorder, relative to the standard gene expression level, i.e., the expression
level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic
epitopes shown in SEQ ID NO: 214 as residues: Val-9 to Cys-14, Pro-42 to Thr-47,
25 Thr-56 to Ala-64, Asp-88 to His-98, Cys-128 to Ser-136, Arg-153 to Trp-161.
Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in liver and gall bladder, combined with the homology
to the diff 40 gene product indicates that polynucleotides and polypeptides
corresponding to this gene are useful for the study and treatment of endocrine and
30 metabolic disorders. polynucleotides and polypeptides corresponding to this gene are
useful for the detection and treatment of liver disorders and cancers. Representative
uses are described in the "Hyperproliferative Disorders", "infectious disease", and

"Binding Activity" sections below, in Example 11, and 27, and elsewhere herein.

Briefly, the protein can be used for the detection, treatment, and/or prevention of hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:101 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1234 of SEQ ID NO:101, b is an integer of 15 to 1248, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:101, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 92

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 3 - 19 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type II membrane proteins.

This gene is expressed primarily in fetal brain and to a lesser extent in pancreas tumor, melanocyte and infant brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural diseases and/or disorders, particularly neurodevelopmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are

useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of developmental disorders of the central nervous system. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:102 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
 5 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1827 of SEQ ID NO:102, b is an integer of 15 to 1841, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:102, and where b is greater than or equal to a + 14.

10 **FEATURES OF PROTEIN ENCODED BY GENE NO: 93**

The translation product of this gene shares sequence homology with a probable membrane protein YGL054c -yeast (*Saccharomyces cerevisiae*). Moreover,

The translation product of this gene also have homology to the human and mouse cornichon protein which is known to be necessary for both anterior-posterior
 15 and dorsal-ventral pattern formation in conjunction with the EGF receptor signaling process (See Genbank Accession Nos. gb|AAC98388.1| (AF104398), and sp|P52159; all references and information available through these accessions are hereby incorporated herein by reference; for example, Cell 81 (6), 967-978 (1995)).

The polypeptide of this gene has been determined to have two transmembrane
 20 domains at about amino acid position 57 - 73, and 121 - 137 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 1 - 14 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type IIIa membrane proteins.

25 In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: YGCEKTTEGGRRRRRRMEAVVFVFSLLDCCAL
 IFLSVYFIITLSDLECDYINARSCSKLNKWWIPELIGHTIVTVLLLSLHWF
 30 IFLNLPPVATWNIYRYIMVPSGNMGVFDPTIEHNRGQLKSHMKEAMIKLGFH
 LLCFFMYLYSMILALIND (SEQ ID NO:362). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in activated T-cells and to a lesser extent in endometrial tumor, T cell helper II cells, microvascular endothelial cells, Raji cells treated with cyclohexamide and umbilical vein endothelial cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, hematopoietic, and vascular diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 216 as residues: Ser-39 to Asn-45, Asn-103 to Ser-109. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in activated T-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of immune disorders involving activated T-cells. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or

other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Moreover, the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:103 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 671 of SEQ ID NO:103, b is an integer of 15 to 685, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:103, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 94

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: ARAPAPSLPPLPSPAPALAPAHSLGLLLGRMS
10 GSSLPSALALSLLLVSGLLPGPAAQNVRVQSGQDQ (SEQ ID NO: 363).
Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in dendritic cells and to a lesser extent in healing abdomen wound, and pancreas islet cell tumor cells.

Therefore, polynucleotides and polypeptides of the invention are useful as
15 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic diseases and/or disorders, particularly wound healing disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential
20 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or
25 cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 217 as residues: Gln-34 to Lys-40. Polynucleotides
30 encoding said polypeptides are also provided.

The tissue distribution in dendritic cells and early healing wound indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating

wounds to enhance the healing process. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or
5 activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene
10 product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and
15 tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits
20 hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their
25 interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
30 related to SEQ ID NO:104 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1154 of SEQ ID NO:104, b is an integer of 15 to 1168, where both a and b correspond to the positions of nucleotide
5 residues shown in SEQ ID NO:104, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 95

Contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of aortic smooth muscle
10 cells to calcium. Thus it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of both smooth muscle cells, and in other cell-lines or tissue cell types. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating smooth muscle cells. Binding of a ligand to a receptor is
15 known to alter intracellular levels of small molecules, such as calcium, potassium and sodium, as well as alter pH and membrane potential. Alterations in small molecule concentration can be measured to identify supernatants which bind to receptors of a particular cell.

This gene is expressed primarily in pancreatic carcinoma, gall bladder and
20 primary dendritic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic and immune diseases and/or disorders, particularly cancers,
25 such as pancreatic carcinoma and gall bladder tumor. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain
30 tissues or cell types (e.g., metabolic, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such

a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 218 as residues: Lys-34 to Ile-41. Polynucleotides
5 encoding said polypeptides are also provided.

The tissue distribution in pancreatic carcinoma and gall bladder indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosing and treating cancer, such as pancreatic carcinoma and gall bladder tumors. Representative uses are described here and elsewhere herein. Alternatively, the
10 detected calcium flux biological activity indicates the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to
15 determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:105 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
25 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1161 of SEQ ID NO:105, b is an integer of 15 to 1175, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:105, and where b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 96

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 10 - 26 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 27 to 48 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ib membrane proteins.

This gene is expressed primarily in osteosarcoma, wilm's tumor, ovarian cancer and in T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammatory diseases and cancers, such as osteosarcoma, wilm's tumor and ovarian cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., skeletal, renal, reproductive, immune, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 219 as residues: Ser-30 to Pro-35. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of inflammatory conditions and cancer, such as osteosarcoma, wilm's tumor and ovarian cancer. Moreover, the expression within cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases

and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

5 Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have
10 applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue
15 differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the
20 protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

25 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:106 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
30 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1007 of SEQ ID NO:106, b is an

integer of 15 to 1021, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:106, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 97

5 In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence: GTSKDCVLYAFLDPGMAVPLFLYIFTLLPLLPF LLSLCFSPLTVKRSSSESSEKSSL (SEQ ID NO: 364). Polynucleotides encoding
10 these polypeptides are also provided.

 This gene is expressed primarily in ovarian cancer.

 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
15 not limited to, ovarian cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types
20 (e.g., reproductive, ovarian, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial amniotic fluid, fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 220 as residues: Thr-28 to Ser-40. Polynucleotides encoding said polypeptides are also provided.

 The tissue distribution in ovarian tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating and diagnosing cancer,
30 e.g., ovarian cancer. Moreover, the expression within cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of

developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern
5 formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of
10 potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types
15 of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new
20 insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or
25 immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:107 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
30 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 816 of SEQ ID NO:107, b is an integer of 15 to 830, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:107, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 98

This gene is expressed primarily in macrophages and breast cancer tissue and to a lesser extent in osteoblasts and smooth muscle.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune system dysfunction; inflammation; breast cancer; cancer; osteoporosis; osteopetrosis; peristaltic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and skeletal systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 221 as residues: Glu-16 to Ala-40. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of a variety of disorders. Expression in macrophages and other hematopoietic cell types indicates that this gene product is involved in the regulation of hematopoietic cell survival, proliferation, differentiation, or activation. It is involved in the control of such processes as immune surveillance, antigen presentation, T cell activation, cytokine release, and inflammation. Expression in breast cancer tissue may possibly correlate with the diagnosis and differentiation of cancerous tissue from normal breast tissue.

Expression in osteoblasts and osteoclasts may implicate this gene product in the process of bone turnover, and target it as a likely candidate for the treatment of osteoporosis and/or osteopetrosis. Finally, expression in smooth muscle may indicate an involvement in the normal function of numerous internal organs and in the function of the digestive system.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:108 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1287 of SEQ ID NO:108, b is an integer of 15 to 1301, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:108, and where b is greater than or equal to a + 14.

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	HDPTK41	209965 06/11/98	pCMVSPORT 3.0	11	1564	1	1564	39	39	124	1	26	27	369
2	HFXGT26	209965 06/11/98	Lambda ZAP II	12	1757	1	1757	13	13	125	1	22	23	85
3	HLTGX30	209965 06/11/98	Uni-ZAP XR	13	1373	1	1373	13	13	126	1	41	42	43
4	HLTHG37	209965 06/11/98	Uni-ZAP XR	14	3740	1908	3740	50	50	127	1	1	2	319
4	HLTHG37	209965 06/11/98	Uni-ZAP XR	109	1932	98	1932	313	313	222	1	35	36	42
5	HNTMZ90	209965 06/11/98	pSPORT1	15	1196	1	1196	282	282	128	1	21	22	45

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of AA of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
6	HPIBX03	209965 06/11/98	Uni-ZAP XR	16	2209	1	2178	81	81	129	1	29	30	709
7	H6EDY30	209965 06/11/98	Uni-ZAP XR	17	1774	1	1774	321	321	130	1	29	30	414
8	HAMGR28	209965 06/11/98	pCMV Sport 3.0	18	1674	47	1674	98	98	131	1	18	19	242
8	HAMGR28	209965 06/11/98	pCMV Sport 3.0	110	1534	1	1534	40	40	223	1	18	19	203
9	HAPNZ94	209965 06/11/98	Uni-ZAP XR	19	2018	255	2018	287	287	132	1	36	37	312
10	HATCP77	209965 06/11/98	Uni-ZAP XR	20	2098	1	2098	37	37	133	1	21	22	182

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
11	HDABR72	209965 06/11/98	pSport1	21	1746	1	1746	28	134	1	29	30	146
12	HDPKB18	209965 06/11/98	pCMVSPORT 3.0	22	2876	1	2876	98	135	1	21	22	122
12	HDPKB18	209965 06/11/98	pCMVSPORT 3.0	111	2871	1	2871	87	224	1	21	22	42
13	HEQCC55	209965 06/11/98	pCMVSPORT 3.0	23	1052	30	1052	62	136	1	27	28	112
13	HEQCC55	209965 06/11/98	pCMVSPORT 3.0	112	1037	1	1037	57	225	1	27	28	155
14	HETDE26	209965 06/11/98	Uni-ZAP XR	24	1541	1	1541	205	137	1	29	30	139

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
15	HOEDH84	209965 06/11/98	Uni-ZAP XR	25	2079	1	2079	256	256	138	1	20	21	404
16	HP1BT55	209965 06/11/98	Uni-ZAP XR	26	1947	129	1947	253	253	139	1	30	31	95
17	HSLCS05	209965 06/11/98	Uni-ZAP XR	27	3379	1	3354	168	168	140	1	23	24	239
18	HDPDD03	209965 06/11/98	pCMVSPORT 3.0	28	2006	1	2006	233	233	141	1	21	22	53
19	HDPDI66	209965 06/11/98	pCMVSPORT 3.0	29	3070	1	3070	93	93	142	1	45	46	66
20	HDTDQ23	209965 06/11/98	pCMVSPORT 2.0	30	2227	1	2206	148	148	143	1	20	21	108

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
20	HDTDQ23	209965 06/11/98	pCMVSPORT 2.0	113	2214	1	2206	148	148	226	1	20	21	73
21	HE2PY40	209965 06/11/98	Uni-ZAP XR	31	1288	1	1288	147	147	144	1	22	23	83
22	HEONM66	209965 06/11/98	pSport1	32	3280	1	3280	89	89	145	1	24	25	166
22	HEONM66	209965 06/11/98	pSport1	114	3300	1	3300	98	98	227	1	20	21	166
23	HKAEG43	209965 06/11/98	pCMVSPORT 2.0	33	1297	1	1297	32	32	146	1	29	30	70
23	HKAEG43	209965 06/11/98	pCMVSPORT 2.0	115	1286	1	1286	21	21	228	1	29	30	70

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of 5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
24	HLHDP65	209965 06/11/98	Uni-ZAP XR	34	2184	1	2184	19	19	147	1	19	20	412
24	HLHDP65	209965 06/11/98	Uni-ZAP XR	116	2189	1	2189	26	26	229	1	21	22	272
25	HLMDO03	209965 06/11/98	Uni-ZAP XR	35	949	1	949	72	72	148	1	45	46	84
26	HMAGK93	209965 06/11/98	Uni-ZAP XR	36	3338	162	1884	164	164	149	1	30	31	153
27	HMEAL02	209965 06/11/98	Lambda ZAP II	37	1563	1	1563	237	237	150	1	33	34	129
28	HMKCH52	209965 06/11/98	pSport1	38	1048	1	1048	53	53	151	1	17	18	61

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	5' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Portion	Last AA of ORF
29	HCEFB69	209965 06/11/98	Uni-ZAP XR	39	1430	1	1430	188	188	152	1	24	224
30	HNFFC43	203027 06/26/98	Uni-ZAP XR	40	2103	209	2058	488	488	153	1	15	68
31	HSPMG77	203027 06/26/98	pSport1	41	2349	1	2349	130	130	154	1	46	83
32	HSQAC69	203027 06/26/98	Uni-ZAP XR	42	1559	1	1559	146	146	155	1	21	60
33	HSTBJ86	203027 06/26/98	Uni-ZAP XR	43	1766	1	1766	120	120	156	1	24	83
34	HILDQR62	203027 06/26/98	pCMVSPORT 3.0	44	2572	427	2572	520	520	157	1	18	161

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	5' NT of Clone Seq.	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
35	HUVDJ43	203027 06/26/98	Uni-ZAP XR	45	526	69	526	89	158	1	31	32	146
36	HADCP14	203027 06/26/98	pSport1	46	1032	1	1032	35	159	1	20	21	142
37	HBXCF95	203027 06/26/98	ZAP Express	47	2680	1	2680	118	160	1	22	23	50
38	HEQBU15	203027 06/26/98	pCMVSPORT 3.0	48	1730	1	1730	56	161	1	26	27	64
39	HL1BD22	203027 06/26/98	Uni-ZAP XR	49	1275	1	1275	53	162	1	39	40	58
40	HOEEU24	203027 06/26/98	Uni-ZAP XR	50	1762	1	1762	113	163	1	21	22	374

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
40	HOEEU24	203027 06/26/98	Uni-ZAP XR	117	1763	1	1763	113	113	230	1	21	22	81
41	HTTBR96	203027 06/26/98	Uni-ZAP XR	51	2059	1	2059	96	96	164	1	26	27	63
42	HWHQS55	203027 06/26/98	pCMV Sport 3.0	52	3282	1	3282	169	169	165	1	26	27	742
43	HCEEK50	203027 06/26/98	Uni-ZAP XR	53	1860	1	1860	233	233	166	1	17	18	213
44	HCWBU94	203027 06/26/98	ZAP Express	54	770	1	770	109	109	167	1	26	27	212
45	HE2NR62	203027 06/26/98	Uni-ZAP XR	55	1093	1	1093	145	145	168	1	38	39	74

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Secreted Portion	Last AA of ORF
46	HHS GH19	203027 06/26/98	Uni-ZAP XR	56	632	1	632	291	291	169	1	15	47
47	HDP GT01	203027 06/26/98	pCMV Sport 3.0	57	2687	138	2687	8	8	170	1	28	87
48	HOB AF11	203027 06/26/98	pBluescript	58	619	153	579	166	166	171	1	30	41
49	HOH CA35	203027 06/26/98	pCMV Sport 2.0	59	1378	1	1378	153	153	172	1	15	47
50	HPM GP24	203027 06/26/98	Uni-ZAP XR	60	1126	1	1126	215	215	173	1	33	232
51	HSD IE16	203027 06/26/98	Uni-ZAP XR	61	2078	1	2078	182	182	174	1	29	44

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
52	HSOBK48	203027 06/26/98	Uni-ZAP XR	62	762	1	762	433	433	175	1	16	17	84
53	HTADH39	203027 06/26/98	Uni-ZAP XR	63	1094	1	1094	173	173	176	1	24	25	65
54	HUSGT36	203027 06/26/98	pSport1	64	1361	1	1361	112	112	177	1	16	17	54
55	HVAAE95	203027 06/26/98	pSport1	65	947	1	947	325	325	178	1	14	15	82
56	HHEAH25	203071 07/27/98	pCMVSPORT 3.0	66	1376	1	1376	43	43	179	1	31	32	330
56	HHEAH25	203071 07/27/98	pCMVSPORT 3.0	118	1375	1	1375	43	43	231	1	31	32	71

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Secreted Portion	Last AA of ORF	
57	HBIIY92	203071 07/27/98	Uni-ZAP XR	67	2434	487	2366	548	548	180	1	29	30	40
58	HCLCW50	203071 07/27/98	Lambda ZAP II	68	1086	1	1086	255	255	181	1	17	18	51
59	HDRMF68	203071 07/27/98	pSport1	69	1262	1	1262	309	309	182	1	22	23	54
60	HOUGG12	203071 07/27/98	Uni-ZAP XR	70	1642	35	1642	116	116	183	1	22	23	61
61	HEEAQ11	203071 07/27/98	Uni-ZAP XR	71	921	1	921	213	213	184	1	28	29	147
62	HEEAZ65	203071 07/27/98	Uni-ZAP XR	72	906	1	906	182	182	185	1	19	20	160

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Portion	Last AA of ORF
63	HEGAN94	203071 07/27/98	Uni-ZAP XR	73	680	1	680	133	133	186	1	23	121
64	HFXBL33	203071 07/27/98	Lambda ZAP II	74	1633	1	1633	152	152	187	1	24	162
65	HLIBD68	203071 07/27/98	pCMVSPORT 1	75	1022	1	1022	186	186	188	1	35	50
66	HLTCO33	203071 07/27/98	Uni-ZAP XR	76	1184	1	1184	80	80	189	1	18	64
67	HL YAC95	203071 07/27/98	pSport1	77	312	1	312	92	92	190	1	16	46
68	HNFGF20	203071 07/27/98	Uni-ZAP XR	78	1370	38	1370	206	206	191	1	45	143

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
69	HNHKS18	203071 07/27/98	Uni-ZAP XR	79	368	1	368	125	125	192	1	36	37	81
70	HSLJW78	203071 07/27/98	Uni-ZAP XR	80	1088	1	1088	159	159	193	1	20	21	44
71	HHFHD01	203071 07/27/98	Uni-ZAP XR	81	1862	1	1862	177	177	194	1	16	17	41
72	HLWAE11	203071 07/27/98	pCMVSPORT 3.0	82	1618	1	1618	85	85	195	1	27	28	259
73	HCYBN55	203071 07/27/98	pBluescript SK-	83	2034	1	1984	341	341	196	1	19	20	117
73	HCYBN55	203071 07/27/98	pBluescript SK-	119	1022	78	1022		3	232	1	1	2	225

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	5' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Secreted Portion	Last AA of ORF
74	HEONX38	203071 07/27/98	pSport1	84	2240	5	2240	23	23	197	1	24	698
74	HEONX38	203071 07/27/98	pSport1	120	2311	1	2311	24	24	233	1	24	314
75	HLDQU79	203071 07/27/98	pCMVSPORT 3.0	85	1488	1	1488	99	99	198	1	24	348
76	HSYBK21	203071 07/27/98	pCMVSPORT 3.0	86	3174	1	1466	119	119	199	1	30	401
77	HELBC12	203071 07/27/98	Uni-ZAP XR	87	2780	2110	2738	120	120	200	1	31	324
78	HTHDS25	203071 07/27/98	Uni-ZAP XR	88	1061	1	1061	70	70	201	1	16	90

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	S' NT of Clone Seq.	S' NT of Clone Seq.	S' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
79	HFIHO70	203071 07/27/98	pSport1	89	1342	1	1271	141	202	1	30	31	243
79	HFIHO70	203071 07/27/98	pSport1	121	1286	1	1279	131	234	1	30	31	93
80	HPMEI86	203071 07/27/98	Uni-ZAP XR	90	770	40	770	50	203	1	30	31	75
81	HSOBV29	203071 07/27/98	Uni-ZAP XR	91	1570	207	1570	244	204	1	24	25	248
82	HWABY10	203071 07/27/98	pCMVSPORT 3.0	92	2950	78	2914	263	205	1	22	23	168
83	HACCI17	203071 07/27/98	Uni-ZAP XR	93	1722	336	1714	461	206	1	24	25	218

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
83	HACCI17	203071 07/27/98	Uni-ZAP XR	122	1380	12	1380	135	135	235	1	24	25	72
84	HAPQT22	203070 07/27/98	Uni-ZAP XR	94	635	1	635	132	132	207	1	17	18	72
85	HDPBO81	203070 07/27/98	pCMVSPORT 3.0	95	3798	1	3798	265	265	208	1	26	27	348
85	HDPBO81	203070 07/27/98	pCMVSPORT 3.0	123	3793	1	3793	255	255	236	1	26	27	348
86	HDPGI49	203070 07/27/98	pCMVSPORT 3.0	96	2683	1	2640	266	266	209	1	29	30	72
87	HDTBV77	203070 07/27/98	pCMVSPORT 2.0	97	2181	1	2181	326	326	210	1	22	23	608

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
88	HF1UE82	203070 07/27/98	pSport1	98	1957	1	1957	24	24	211	1	23	24	251
89	HHEND31	203070 07/27/98	pCMVSPORT 3.0	99	1112	1	1112	109	109	212	1	25	26	225
90	HKMND01	203069 07/27/98	pBluescript	100	887	1	887	23	23	213	1	26	27	50
91	HLDBI84	203069 07/27/98	pCMVSPORT 3.0	101	1248	1	1248	50	50	214	1	35	36	171
92	HLTEK17	203069 07/27/98	Uni-ZAP XR	102	1841	1	1841	112	112	215	1	13	14	47
93	HEBEJ18	203069 07/27/98	Uni-ZAP XR	103	685	7	649	51	51	216	1	15	16	139

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Portion	Last AA of ORF	
94	HMEAI48	203069 07/27/98	Lambda ZAP II	104	1168	1	1168	95	95	217	1	29	30	40
95	HNHGN91	203069 07/27/98	Uni-ZAP XR	105	1175	161	1175	184	184	218	1	24	25	51
96	HODAE92	203069 07/27/98	Uni-ZAP XR	106	1021	1	1021	123	123	219	1	29	30	48
97	HODDF13	203069 07/27/98	Uni-ZAP XR	107	830	1	830	46	46	220	1	27	28	41
98	HCDCF30	203027 06/26/98	Uni-ZAP XR	108	1301	102	1301	151	151	221	1	14	15	40

Table 1 summarizes the information corresponding to each "Gene No." described above. The nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the "cDNA clone ID" identified in Table 1 and, in some cases, from additional related DNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X.

The cDNA Clone ID was deposited on the date and given the corresponding deposit number listed in "ATCC Deposit No:Z and Date." Some of the deposits contain multiple different clones corresponding to the same gene. "Vector" refers to the type of vector contained in the cDNA Clone ID.

"Total NT Seq." refers to the total number of nucleotides in the contig identified by "Gene No." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." and the "3' NT of Clone Seq." of SEQ ID NO:X. The nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep."

The translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

The first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." The predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion." Finally, the amino acid position of SEQ ID NO:Y of the last amino acid in the open reading frame is identified as "Last AA of ORF."

SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization

probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID
5 NO:Y may be used to generate antibodies which bind specifically to the secreted proteins encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or
10 deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

15 Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC,
20 as set forth in Table 1. The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a
25 suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or the deposited clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed
30 herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are species homologs. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for the desired homologue.

5 The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

10 The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification , such as multiple histidine residues, or an additional sequence for stability during
15 recombinant production.

The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified by the one-step method described in Smith and Johnson, Gene 67:31-40
20 (1988). Polypeptides of the invention also can be purified from natural or recombinant sources using antibodies of the invention raised against the secreted protein in methods which are well known in the art.

Signal Sequences

25 Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, Virus Res. 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, Nucleic Acids Res. 14:4683-4690 (1986) uses the
30 information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of

these methods is in the range of 75-80%. (von Heinje, supra.) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.

In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., Protein Engineering 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results shown in Table 1.

As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., + or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Polynucleotide and Polypeptide Variants

"Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

By a polynucleotide having a nucleotide sequence at least, for example, 95%

"identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence shown in Table 1, the ORF (open reading frame), or any fragement specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence

that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid.

These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

- 5 As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequences shown in Table 1 or to the amino acid sequence encoded by deposited DNA clone can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity.
- 10 Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.
- 15 If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and
- 20
- 25
- 30

C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

5 For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

15 The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as E. coli).

30 Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an

organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level.

Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

5 Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., J. Biol. Chem. 268: 2984-2988
10 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

15 Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over
20 the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in
25 activity from wild-type.

 Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted
30 form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic

activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, 5 inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

10 The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these 15 positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. 20 For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are 25 surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions 30 involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of

the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention
5 include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for
10 example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of
15 charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev.
20 Therapeutic Drug Carrier Systems 10:307-377 (1993).)

A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of the present invention having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid
25 substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course, in order of ever-increasing preference, it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of the present invention, which contains at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1
30 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of the present invention or fragments thereof (e.g., the mature form and/or other fragments described herein), is

1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

Polynucleotide and Polypeptide Fragments

5 In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence contained in the deposited clone or shown in SEQ ID NO:X. The short nucleotide fragments are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length. A fragment "at least 20 nt
10 in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in the deposited clone or the nucleotide sequence shown in SEQ ID NO:X. These nucleotide fragments are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

15 Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments having a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-
20 1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, or 2001 to the end of SEQ ID NO:X or the cDNA contained in the deposited clone. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.
25 Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed herein.

 In the present invention, a "polypeptide fragment" refers to a short amino acid sequence contained in SEQ ID NO:Y or encoded by the cDNA contained in the
30 deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the

invention, include, for example, fragments from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotide fragments encoding these polypeptide fragments are also preferred.

Also preferred are polypeptide and polynucleotide fragments characterized by structural or functional domains, such as fragments that comprise alpha-helix and alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions. Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotide fragments encoding these domains are also contemplated.

Other preferred fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Epitopes & Antibodies

In the present invention, "epitopes" refer to polypeptide fragments having antigenic or immunogenic activity in an animal, especially in a human. A preferred embodiment of the present invention relates to a polypeptide fragment comprising an epitope, as well as the polynucleotide encoding this fragment. A region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." In contrast, an "immunogenic epitope" is defined as a part of a protein that elicits an antibody response. (See, for instance, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998-4002 (1983).)

Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

In the present invention, antigenic epitopes preferably contain a sequence of at least seven, more preferably at least nine, and most preferably between about 15 to about 30 amino acids. Antigenic epitopes are useful to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe, J. G. et al., Science 219:660-666 (1983).)

Similarly, immunogenic epitopes can be used to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow, M. et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle, F. J. et al., J. Gen. Virol. 66:2347-2354 (1985).) A preferred immunogenic epitope includes the secreted protein. The immunogenic epitopes may be presented together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse) or, if it is long enough (at least about 25 amino acids), without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting.)

As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules as well as antibody fragments (such as, for example, Fab and F(ab')₂ fragments) which are capable of specifically binding to protein. Fab and F(ab')₂ fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody. (Wahl et al., J. Nucl. Med. 24:316-325 (1983).) Thus, these

fragments are preferred, as well as the products of a FAB or other immunoglobulin expression library. Moreover, antibodies of the present invention include chimeric, single chain, and humanized antibodies.

5 **Fusion Proteins**

Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second
10 protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous
15 functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the
20 polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

Moreover, polypeptides of the present invention, including fragments, and
25 specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-
30 polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., Nature 331:84-86 (1988).) Fusion proteins having disulfide-linked dimeric structures (due to the

IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995).)

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion
5 proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified,
10 would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol.
15 Chem. 270:9459-9471 (1995).)

Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue,
20 Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767
25 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

Vectors, Host Cells, and Protein Production

30 The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral

vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

5 The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

10 The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding
15 portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin
20 resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in E. coli and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as E. coli, Streptomyces and Salmonella typhimurium cells; fungal cells, such as yeast cells; insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as
25 CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-
9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and
30 ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1

and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods
5 are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

10 A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most
15 preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention, and preferably the secreted form, can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical
20 synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also
25 include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some
30 proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding
5 sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with the polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences
10 via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their
15 entireties).

Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as
20 reagents. The following description should be considered exemplary and utilizes known techniques.

The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat
25 polymorphisms), are presently available. Each polynucleotide of the present invention can be used as a chromosome marker.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be selected using computer analysis so that primers do not span more than one predicted
30 exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids

containing the human gene corresponding to the SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome specific-cDNA libraries.

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes). Preferred polynucleotides correspond to the noncoding regions of the cDNAs because the coding sequences are more likely conserved within gene families, thus increasing the chance of cross hybridization during chromosomal mapping.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) .) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or

translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide
5 and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using
10 polynucleotides of the present invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Both methods
15 rely on binding of the polynucleotide to DNA or RNA. For these techniques, preferred polynucleotides are usually 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene
20 Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can
25 be used to design antisense or triple helix polynucleotides in an effort to treat disease.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate
30 manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more
5 restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

10 The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a
15 unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological
20 samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with
25 one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a
30 particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the

present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

In the very least, the polynucleotides of the present invention can be used as
5 molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an
10 immune response.

Uses of the Polypeptides

Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

15 A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. (Jalkanen, M., et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell . Biol. 105:3087-3096 (1987).) Other antibody-based methods useful for detecting protein gene
20 expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (¹²⁵I, ¹²¹I), carbon (¹⁴C), sulfur (³⁵S), tritium (³H), indium (¹¹²In), and technetium (^{99m}Tc), and fluorescent labels, such as fluorescein and rhodamine, and
25 biotin.

In addition to assaying secreted protein levels in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which
30 emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as

deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I , ^{112}In , $^{99\text{m}}\text{Tc}$), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously, or intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of $^{99\text{m}}\text{Tc}$. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).)

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder.

Moreover, polypeptides of the present invention can be used to treat disease. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B), to inhibit the activity of a polypeptide (e.g., an oncogene), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

Biological Activities

The polynucleotides and polypeptides of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides could be used to treat the associated disease.

Immune Activity

A polypeptide or polynucleotide of the present invention may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, a polynucleotide or polypeptide of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

A polynucleotide or polypeptide of the present invention may be useful in treating or detecting deficiencies or disorders of hematopoietic cells. A polypeptide or polynucleotide of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

Moreover, a polypeptide or polynucleotide of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, a polynucleotide or polypeptide of the present invention could be used to treat blood coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, a polynucleotide or polypeptide of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

A polynucleotide or polypeptide of the present invention may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Examples of autoimmune disorders that can be treated or detected by the present invention include, but are not limited to: Addison's Disease, hemolytic

anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, 5 Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by a polypeptide 10 or polynucleotide of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

A polynucleotide or polypeptide of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ 15 rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of 20 T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, a polypeptide or polynucleotide of the present invention may also be used to modulate inflammation. For example, the polypeptide or polynucleotide may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic 25 and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or 30 IL-1.)

Hyperproliferative Disorders

A polypeptide or polynucleotide can be used to treat or detect hyperproliferative disorders, including neoplasms. A polypeptide or polynucleotide of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, a polypeptide or polynucleotide of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but are not limited to neoplasms located in the: abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstrom's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

Infectious Disease

A polypeptide or polynucleotide of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response.

Alternatively, the polypeptide or polynucleotide of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of viruses, include, but are not limited to the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Nocardia), Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Pasteurellaceae Infections (e.g., Actinobacillus, Haemophilus, Pasteurella), Pseudomonas, Rickettsiaceae,

Chlamydiaceae, Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas. These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Preferably, treatment using a polypeptide or polynucleotide of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

A polynucleotide or polypeptide of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, a polynucleotide or polypeptide of the present invention may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. A polynucleotide or polypeptide of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using a polynucleotide or polypeptide of the present invention to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotide or polypeptide of the present invention.

Chemotaxis

A polynucleotide or polypeptide of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or
5 endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

A polynucleotide or polypeptide of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used
10 to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

15 It is also contemplated that a polynucleotide or polypeptide of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, a polynucleotide or polypeptide of the present invention could be used as an inhibitor of chemotaxis.

20 Binding Activity

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples
25 of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology
30 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable

of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide, either as a secreted protein or on the cell
5 membrane. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

10 The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations,
15 polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

20 Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

All of these above assays can be used as diagnostic or prognostic markers.
25 The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptide from suitably manipulated cells or tissues.

30 Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a

candidate binding compound with a polypeptide of the invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

Other Activities

A polypeptide or polynucleotide of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide or polynucleotide of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide or polynucleotide of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide or polynucleotide of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, cardiac rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide or polynucleotide of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

Other Preferred Embodiments

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only
5 A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the material deposited with the American Type Culture Collection and given the ATCC Deposit Number shown in Table 1 for said
10 cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the deposit given the
15 ATCC Deposit Number shown in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide
20 sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human
25 cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological
30 sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X

wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing a nucleotide sequence of at least one
5 nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid
10 molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA
15 molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence
20 selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table
1.

25 The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

30 Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a

wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing a nucleotide sequence of at least one
5 nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid
10 molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA
15 molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence
20 selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

25 The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

30 Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a

biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; 5 and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at 10 least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise 15 a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 20 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the 25 amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the 30 Open Reading Frame as set forth for SEQ ID NO:Y in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

5 Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

10 Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

15 Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

20 Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

25 Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

30 Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1

and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence
5 selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

10 Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: an amino
15 acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method of making a recombinant vector comprising
20 inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising
25 culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of
30 SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is

defined in Table 1; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The isolated polypeptide produced by this method is also preferred.

5 Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

10 Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

Examples

15 Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage
20 vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

25	<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited</u>
	<u>Plasmid</u>	
	Lambda Zap	pBluescript (pBS)
	Uni-Zap XR	pBluescript (pBS)
	Zap Express	pBK
30	lafmid BA	plafmid BA
	pSport1	pSport1
	pCMVSPORT 2.0	pCMVSPORT 2.0

pCMVSPORT 3.0

pCMVSPORT 3.0

pCR[®]2.1pCR[®]2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128,256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Altting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Altting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS-. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the fl origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

Vectors pSPORT1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lacmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR[®]2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional

plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises a mixture of approximately equal amounts (by weight) of about 50
5 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly
10 isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ^{32}P - γ -ATP using T4 polynucleotide
15 kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above.
20 The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to
25 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain
30 reaction is carried out under routine conditions, for instance, in 25 μl of reaction mixture with 0.5 μg of the above cDNA template. A convenient reaction mixture is 1.5-5 mM MgCl_2 , 0.01% (w/v) gelatin, 20 μM each of dATP, dCTP, dGTP, dTTP, 25

pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with
5 expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes,
10 and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a
15 population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

20 This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order
25 to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is
30 used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of

the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

- 5 A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

Example 3: Tissue Distribution of Polypeptide

- 10 Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by, among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P³² using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After
15 labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is then used to examine various human tissues for mRNA expression.

- 20 Multiple Tissue Northern (MTN) blots containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70°C overnight, and the films developed according to standard procedures.

25

Example 4: Chromosomal Mapping of the Polynucleotides

- 30 An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing

individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

5

Example 5: Bacterial Expression of a Polypeptide

A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers
10 used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a
15 bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at
20 the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and
25 confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.⁶⁰⁰) of between 0.4 and 0.6. IPTG
30 (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1

mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The

origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

The following alternative method can be used to purify a polypeptide expressed in *E. coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without
5 mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive
10 Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4
15 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using
20 a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the
25 above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 µg of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 7: Cloning and Expression of a Polypeptide in a Bacul virus Expression System

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector
5 contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak
10 *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such
15 as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

20 Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in Table 1, is amplified using the PCR protocol described in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP)
25 to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a
30 commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

5 The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by
10 gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five µg of a plasmid containing the polynucleotide is co-transfected with 1.0 µg of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method
15 described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One µg of BaculoGold™ virus DNA and 5 µg of the plasmid are mixed in a sterile well of a microtiter plate containing 50 µl of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 µl Lipofectin plus 90 µl Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the
20 transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

25 After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell
30 culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then

resuspended in a microcentrifuge tube containing 200 μ l of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

5 To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and
10 cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 μ Ci of 35 S-methionine and 5 μ Ci 35 S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

15 Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

Example 8: Expression of a Polypeptide in Mammalian Cells

20 The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient
25 transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV, HIV and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

30 Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109),

pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

5 Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

 The transfected gene can also be amplified to express large amounts of the
10 encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker
15 is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the
20 production of proteins.

 Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No.209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the
25 CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

30 Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be
5 modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

10 The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

15 Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five μ g of the expression plasmid pC6 is cotransfected with 0.5 μ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded
20 in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM,
25 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 μ M, 2 μ M, 5 μ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 -
30 200 μ M. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

Example 9: Protein Fusions

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see
5 also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the half-life time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create
10 chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

15 Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion
20 can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will
25 not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)
30

Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAAACCTCACACATGCCCACCGTGC
CCAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCAAAA
CCCAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTACATGCGTGGT
GGTGGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGG
5 ACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTA
CAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACT
GGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCA
ACCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAG
10 GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGT
GGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCT
CCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTG
GACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG
15 GTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)

Example 10: Production of an Antibody from a Polypeptide

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) For example, cells expressing a
20 polypeptide of the present invention is administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

25 In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., Nature 256:495 (1975); Köhler et al., Eur. J. Immunol. 6:511 (1976); Köhler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell
30 Hybridomas, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in

any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

5 The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as
10 described by Wands et al. (Gastroenterology 80:225-232 (1981).) The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

 Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method
15 makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody
20 whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

 It will be appreciated that Fab and F(ab')₂ and other fragments of the
25 antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')₂ fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic
30 chemistry.

 For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced

using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

Example 11: Production Of Secreted Protein For High-Throughput Screening

Assays

The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described in Examples 13-20.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at 2×10^5 cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8 or 9, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45

minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37°C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or CHO-5 media (116.6 mg/L of CaCl₂ (anhyd); 0.00130 mg/L CuSO₄·5H₂O; 0.050 mg/L of Fe(NO₃)₃·9H₂O; 0.417 mg/L of FeSO₄·7H₂O; 311.80 mg/L of KCl; 28.64 mg/L of MgCl₂; 48.84 mg/L of MgSO₄; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO₃; 62.50 mg/L of NaH₂PO₄·H₂O; 71.02 mg/L of Na₂HPO₄; .4320 mg/L of ZnSO₄·7H₂O; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H₂O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H₂O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H₂O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H₂O; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319

mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B₁₂; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of

5 Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for

10 endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37°C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

15 On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13-20.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the

20 polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

25 **Example 12: Construction of GAS Reporter Construct**

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The

30 binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six

members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at
5 higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2,
10 Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two
15 groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

20 Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the
25 proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

	<u>Ligand</u>	<u>JAKs</u>				<u>STATs</u>	<u>GAS(elements) or ISRE</u>
		<u>tyk2</u>	<u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>		
<u>IFN family</u>							
5	IFN-a/B	+	+	-	-	1,2,3	ISRE
	IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)
	Il-10	+	?	?	-	1,3	
<u>gp130 family</u>							
10	IL-6 (Pleiotrophic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
	Il-11(Pleiotrophic)	?	+	?	?	1,3	
	OnM(Pleiotrophic)	?	+	+	?	1,3	
	LIF(Pleiotrophic)	?	+	+	?	1,3	
	CNTF(Pleiotrophic)	-/+	+	+	?	1,3	
15	G-CSF(Pleiotrophic)	?	+	?	?	1,3	
	IL-12(Pleiotrophic)	+	-	+	+	1,3	
<u>g-C family</u>							
	IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
20	IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
	IL-7 (lymphocytes)	-	+	-	+	5	GAS
	IL-9 (lymphocytes)	-	+	-	+	5	GAS
	IL-13 (lymphocyte)	-	+	?	?	6	GAS
	IL-15	?	+	?	+	5	GAS
25							
<u>gp140 family</u>							
	IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
	IL-5 (myeloid)	-	-	+	-	5	GAS
	GM-CSF (myeloid)	-	-	+	-	5	GAS
30							
<u>Growth hormone family</u>							
	GH	?	-	+	-	5	

PRL	?	+/-	+	-	1,3,5
-----	---	-----	---	---	-------

EPO	?	-	+	-	5
-----	---	---	---	---	---

GAS(B-CAS>IRF1=IFP>>Ly6)

Receptor Tyrosine Kinases

5	EGF	?	+	+	-	1,3
---	-----	---	---	---	---	-----

GAS (IRF1)

	PDGF	?	+	+	-	1,3
--	------	---	---	---	---	-----

	CSF-1	?	+	+	-	1,3
--	-------	---	---	---	---	-----

GAS (not IRF1)

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCCGGAAATCTAGATTTCCCGGAAATGATTTCCCG
GAAATGATTTCCCGGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCCGGAAATCTAGATTTCCCGGAAATGATTTCCCGGAAA
TGATTTCCCGGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCG
CCCCTAACTCCGCCATCCCGCCCCTAACTCCGCCCAGTTCGCCCATTTCT
CCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCC
TCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCT
AGGCTTTTGCAAAAAGCTT:3' (SEQ ID NO:5)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not
5 contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance
10 gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS
15 with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-
20 2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

Example 13: High-Throughput Screening Assay for T-cell Activity.

25 The following protocol is used to assess T-cell activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells
30 (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately
5 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells
10 containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.
15 During the incubation period, count cell concentration, spin down the required number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final concentration of 10^7 cells/ml. Then add 1ml of 1×10^7 cells in OPTI-MEM to T25 flask and incubate at 37°C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

20 The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing a polypeptide as produced by the protocol described in Example 11.

On the day of treatment with the supernatant, the cells should be washed and
25 resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells
30 into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the
5 assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and
10 stored at -20°C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4°C and serve as a source of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the
15 positive control wells.

The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

Example 14: High-Throughput Screening Assay Identifying Myeloid Activity

20 The following protocol is used to assess myeloid activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell
25 used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest 2×10^7 U937 cells and
30 wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing

10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM
5 KCl, 375 uM Na₂HPO₄·7H₂O, 1 mM MgCl₂, and 675 uM CaCl₂. Incubate at 37°C for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37°C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400
10 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting 1×10^8 cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of 5×10^5 cells/ml. Plate 200 ul cells per well in
15 the 96-well plate (or 1×10^5 cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example 11. Incubate at 37°C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant
20 according to the protocol described in Example 17.

Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes,
25 EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat pheochromocytoma cells) are known to proliferate and/or
30 differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor).

The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

The EGR/SEAP reporter construct can be assembled by the following
5 protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:6)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

10 Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

15 To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker)
20 containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

25 Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

30 To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS

(Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count
5 the cell number and add more low serum medium to reach final cell density as 5×10^5 cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to 1×10^5 cells/well). Add 50 ul supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR
10 can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 17.

Example 16: High-Throughput Screening Assay for T-cell Activity

15 NF- κ B (Nuclear Factor κ B) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF- κ B regulates the expression of genes involved in immune cell activation, control of
20 apoptosis (NF- κ B appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- κ B is retained in the cytoplasm with I- κ B (Inhibitor κ B). However, upon stimulation, I- κ B is phosphorylated and degraded, causing NF- κ B to shuttle to the nucleus, thereby activating transcription of target
25 genes. Target genes activated by NF- κ B include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF- κ B promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF- κ B would be useful in
30 treating diseases. For example, inhibitors of NF- κ B could be used to treat those

diseases related to the acute or chronic activation of NF- κ B, such as rheumatoid arthritis.

To construct a vector containing the NF- κ B promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF- κ B binding site (GGGGACTTTCCC) (SEQ ID NO:8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:
5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGGAC
TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTGTCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene)

Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGGACTTTCC
ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCC
ATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTTCTCCGCCCCATGGCTGA
CTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCTCGGCCTCTGAGCTA
TTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAA
GCTT:3' (SEQ ID NO:10)

Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF- κ B/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF- κ B/SV40/SEAP cassette is removed from the above NF- κ B/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly,

the NF- κ B/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF- κ B/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 13. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

Example 17: Assay for SEAP Activity

As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 μ l of 2.5x dilution buffer into Optiplates containing 35 μ l of a supernatant. Seal the plates with a plastic sealer and incubate at 65°C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 μ l Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 μ l Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5

13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

Example 18: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO₂ incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37°C in a CO₂ incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10⁶ cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37°C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10⁶ cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4. The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event which has resulted in an increase in the intracellular Ca^{++} concentration.

Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of activating tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed with PBS and stored at 4°C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 11, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na₃VO₄, 2 mM Na₄P₂O₇ and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4°C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by
5 determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

10 The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg₂⁺ (5mM ATP/50mM MgCl₂), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl₂, 5 mM MnCl₂, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the
15 components gently and preincubate the reaction mix at 30°C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction
20 mixture to a microtiter plate (MTP) module and incubating at 37°C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37°C for one hour. Wash the well as
25 above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of
30 tyrosine kinase activity.

Example 20: High-Throughput Screening Assay Identifying Phosphorylation Activity

As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 19, an assay which detects activation
5 (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other
10 phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G
15 plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at
20 4°C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts
25 filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place
of A431 extract. Plates are then treated with a commercial polyclonal (rabbit)
30 antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive

incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation.

5 **Example 21: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide**

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA
10 is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; and 60-120 seconds at 70°C, using buffer solutions described in Sidransky, D., et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4
15 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

20 PCR products is cloned into T-tailed vectors as described in Holton, T.A. and Graham, M.W., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining
25 alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Mannheim), and FISH performed as described in Johnson, Cg. et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to
30 the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for

precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson, Cv. et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and
5 chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

10
Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide
15 is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with
20 specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample
25 containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature.

30 The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale).
5 Interpolate the concentration of the polypeptide in the sample using the standard curve.

Example 23: Formulating a Polypeptide

10 The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective
15 amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1 $\mu\text{g/kg/day}$ to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01
20 mg/kg/day , and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the secreted polypeptide is typically administered at a dose rate of about 1 $\mu\text{g/kg/hour}$ to about 50 $\mu\text{g/kg/hour}$, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of
25 treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal
30 patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to

modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., *Biopolymers* 22:547-556 (1983)), poly (2-hydroxyethyl methacrylate) (R. Langer et al., *J. Biomed. Mater. Res.* 15:167-277 (1981), and R. Langer, *Chem. Tech.* 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D-(-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE 3,218,121; Epstein et al., *Proc. Natl. Acad. Sci. USA* 82:3688-3692 (1985); Hwang et al., *Proc. Natl. Acad. Sci. USA* 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's

solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in

the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other
5 therapeutic compounds.

Example 24: Method of Treating Decreased Levels of the Polypeptide

It will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by
10 administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

15 For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

20 **Example 25: Method of Treating Increased Levels of the Polypeptide**

Antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

25 For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 23.

30

Example 26: Method of Treatment Using Gene Therapy

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

15

Example 27: Method of Treatment Using Gene Therapy - In Vivo

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata H. et al. (1997) Cardiovasc. Res. 35(3):470-479, Chao J et al. (1997) Pharmacol. Res. 35(6):517-522, Wolff J.A. (1997) Neuromuscul. Disord. 7(5):314-318, Schwartz B. et al. (1996) Gene Ther. 3(5):405-411, Tsurumi Y. et al. (1996) Circulation 94(12):3281-3290 (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The

30

polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely

differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or
5 RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence
10 can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues; throat or
15 mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard
20 recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on
25 the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

30 After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A

time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice.

- 5 The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

Example 28: Transgenic Animals.

- 10 The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are
15 used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

- Any technique known in the art may be used to introduce the transgene (*i.e.*, polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear
20 microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic
25 stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, *e.g.*, Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-
30 mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse

transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 29: Knock-Out Animals.

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., Nature 317:230-234 (1985); Thomas & Capecchi, Cell 51:503-512 (1987); Thompson et al., Cell 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in

the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (*e.g.*, see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

10 In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (*e.g.*, knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (*i.e.*, animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (*e.g.*, lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, *e.g.*, by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, *e.g.*, in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, *e.g.*, genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and

Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

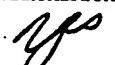
The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties.

Applicant's or agent's file reference number	PZ031PCT	International application No.	Unassigned
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>259</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit July 27, 1998	Accession Number 203070
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	


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(PCT Rule 13bis)


A. The indications made below relate to the microorganism referred to in the description on page <u>260</u> , line <u>N/A</u>	
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Date of deposit July 27, 1998	Accession Number 203069
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(PCT Rule 13bis)


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Date of deposit July 27, 1998	Accession Number 203071
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
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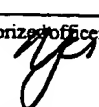
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What Is Claimed Is:

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:
 - (a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
 - (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
 - (c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
 - (d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
 - (e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X, having biological activity;
 - (f) a polynucleotide which is a variant of SEQ ID NO:X;
 - (g) a polynucleotide which is an allelic variant of SEQ ID NO:X;
 - (h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;
 - (i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.
2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.

3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.
4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.
5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.
6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.
7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.
8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.
9. A recombinant host cell produced by the method of claim 8.
10. The recombinant host cell of claim 9 comprising vector sequences.
11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

- (a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
 - (b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;
 - (c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
 - (d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
 - (e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
 - (f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
 - (g) a variant of SEQ ID NO:Y;
 - (h) an allelic variant of SEQ ID NO:Y; or
 - (i) a species homologue of the SEQ ID NO:Y.
12. The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.
13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.
14. A recombinant host cell that expresses the isolated polypeptide of claim 11.
15. A method of making an isolated polypeptide comprising:
- (a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and
 - (b) recovering said polypeptide.
16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

(a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

22. A method of identifying an activity in a biological assay, wherein the method comprises:

(a) expressing SEQ ID NO:X in a cell;

(b) isolating the supernatant;

(c) detecting an activity in a biological assay; and

(d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 20.

<110> Human Genome Sciences, Inc.

<120> 98 Human Secreted Proteins

<130> PZ031.PCT

<140> Unassigned

<141> 1999-07-28

<150> 60/094,657

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<170> PatentIn Ver. 2.0

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agaaaaccat	ctccaaagcc	aaagggcagc	cccgagaacc	acaggtgtac	accctgcccc	420
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acaagagcag	gtggcagcag	gggaacgtct	tctcatgctc	cgtgatgcat	gaggctctgc	660
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gactctagag	gat					733

<210> 2

<211> 5

<212> PRT

<213> Homo sapiens

<220>

<221> Site

<222> (3)

<223> Xaa equals any of the twenty naturally occurring L-amino acids

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1 5

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<212> DNA

<213> Homo sapiens

<400> 3

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<211> 2018

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<222> (2012)

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<222> (2014)

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<222> (2016)

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<212> DNA

<213> Homo sapiens

<400> 20

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<211> 1746

<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

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<211> 1947

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<213> Homo sapiens

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 <213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<211> 1297

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<210> 35

<211> 949

<212> DNA

<213> Homo sapiens

<400> 35

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949

<210> 36
<211> 3338
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>
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<223> n equals a,t,g, or c

<220>
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<223> n equals a,t,g, or c

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<210> 37

<211> 1563

<212> DNA

<213> Homo sapiens

<400> 37

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ccc						1560
						1563

<210> 38

<211> 1048
 <212> DNA
 <213> Homo sapiens

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 aaaaaaaaaa aaaaaaaaaa gcggccgc 1048

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 <211> 1430
 <212> DNA
 <213> Homo sapiens

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<210> 40
 <211> 2103

<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (2102)
<223> n equals a,t,g, or c

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<211> 2349
<212> DNA
<213> Homo sapiens

<400> 41
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<210> 42

<211> 1559

<212> DNA

<213> Homo sapiens

<400> 42

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<210> 43

<211> 1766

<212> DNA

<213> Homo sapiens

<400> 43

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<210> 44

<211> 2572

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (2527)

<223> n equals a,t,g, or c

<400> 44

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<210> 45

<211> 526

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (66)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (106)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (484)

<223> n equals a,t,g, or c

<400> 45

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sccttgtgga	ratcttttaa	ctggtcagca	awtwtcaaac	gaaatctcca	aacaggaaat	480
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<210> 46

<211> 1032

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (974)

<223> n equals a,t,g, or c

<400> 46

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<210> 47

<211> 2680

<212> DNA

<213> Homo sapiens

<400> 47
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<210> 48

<211> 1730

<212> DNA

<213> Homo sapiens

<400> 48

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<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

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<211> 2059

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

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<213> Homo sapiens

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gatgctaaaa	gctatccagg	attttgtttc	tgtttgtttt	aaattttgtg	gttccttccc	960
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aaaaaaaaact	cga					1093

<210> 56

<211> 632

<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (29)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (46)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (94)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (162)
<223> n equals a,t,g, or c

<400> 56
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cggctcgtat gttgtgtgga attgtgacgg atancaattt cacacaggaa acagctatgc 120
catgattacg ccaagctcga aattaaccct cactaaaggg ancaaaagct ggagctccac 180
cgcggtggcg gccgctctag aactagtgga tccccgggc tgcaggaatt cggcacgaga 240
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gcctgcctca atgtatatatt atttcttttg aaacaaaaag gttctggaaa ctgtttttct 420
gtagctttta atgaataggt gagcaaaatc tatatgggat gtaatttttt tgttcagtct 480
cttaaaaaat actttgtttt ggtacatttg gttgtgcttg tggggaaaat aaaaacgcag 540
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aataaaaaaa aaaaaaaaaa gtcgagggg gg 632

<210> 57
<211> 2687
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1614)
<223> n equals a,t,g, or c

<400> 57
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cccagtggtg ctggctccctg gtgatttggg taaccaactg gaagccaagc tggacaagcc 180
gacagtggtg cactacctct gctccaagaa gaccgaaagc tacttcacaa tctggctgaa 240
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acaacaaaac atccagggcc acccagtttc ctgatggtgt ggatgtacgt gtccctggct 360
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tccacaccat ggtggagagc cttgtgggct ggggctacac acggggtgag gatgtccgag 480
gggctcccta tgactggcgc cgagcccaa atgaaaacgg gccctacttc ctggccctcc 540
gcgagatgat cgaggagatg taccagctgt atgggggccc cgtggtgctg gttgccaca 600
gtatgggcaa catgtacacg ctctactttc tgcagcggca gccgcaggcc tgggaargaca 660

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caccagactc	cttctactat	gagagcttcc	atgacgtga	ccctaaaatc	tgctttgggtg	1080
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gccccacatg	gggctctgag	caggctgtat	ctggattctg	gcaataaaaag	tactctggat	2640
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<210> 58

<211> 619

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (526)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (619)

<223> n equals a,t,g, or c

<400> 58

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ccttggctcc	ctgctgccct	caggataaag	tctggacccc	tcagcatggc	ttgtgagact	180
catggtgtcc	ttgtccctgc	tcacctctct	ggctctcatca	cttgcccttct	tgcattcttg	240
gtcccagcct	cctgtatcca	gagatgcagt	ggctctccat	tgccactctg	attcctcctt	300
tcttttggtc	acagagaaaag	ggtactttct	ctgtcaaatc	tcaacttaga	cttgacttcc	360
tccaaggagc	tttgggtata	ctctctcctc	ccgacccccca	ccctggcata	ctacacagat	420

cactctgggc	tcacttgcct	gcctaattggt	catctcccca	gtagactgta	agctccttga	480
gggcaaggat	tgtgttgga	tttttgtatt	aacagtgcct	ggcttngtgc	ctggcaccta	540
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aaaaaaaaa	aaaaaaaaa					619

<210> 59
 <211> 1378
 <212> DNA
 <213> Homo sapiens

<400> 59	
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taattacagg	cttggcagaa
aaatacaact	gtcctctaca
gattaggttc	atacttttgt
gtgcagcttc	attaaggggt
tccatgtttt	tactctccca
ttctcctctc	tctctgatta
cagcgtcttc	cttcttcagt
catcatttaa	aaattctcct
ctcccttagc	tgagggtggt
tgtgggtttt	tccagtttct
gttgtatttt	agattcaaat
ctttgatgct	ctcttcatag
aggggaatttt	cgcaaaaaaa
tttcaaatac	catatttgc
gttcttctaa	atttgtaaat
tattcatttg	cagttggatg
ctacaggtaa	ttttcggaca
taattctctac	aggatcatgg
aaattacagg	ctctattaac
tcccgggtcg	acgagctcac
	tagtcggcgg
	ccgctctaga
	ggatccctcg
	agggggccc
	60
	120
	180
	240
	300
	360
	420
	480
	540
	600
	660
	720
	780
	840
	900
	960
	1020
	1080
	1140
	1200
	1260
	1320
	1378

<210> 60
 <211> 1126
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (21)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (35)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (49)
 <223> n equals a,t,g, or c

<220>
 <221> SITE

<222> (99)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1012)

<223> n equals a,t,g, or c

<400> 60

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tatgcccacg attacgcca gttcgaaatt aaccctcant aaaggaccaa aagtgaagtt	120
ccaccgcggt gccggcccg cctagaaact agtggatccc ccgggctgca ggaattcggc	180
acgagccggg ccgtaccgcc aggcgatcgc gctgatggcg gcgctggcag cagcggccaa	240
gaaggtgtgg agcgcgcggc ggctgctggt gctgctgttc acgccgctcg cgctgctgcc	300
ggtggtcttc gccctcccg ccaaggaagg ccgctgcttg tttgtcatcc tgctcatggc	360
ggtgtactgg tgcacggagg cctgcccgt ctcagtgcgc gcgctgctgc ccatcgctct	420
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caacttcttc ttcctcagtg ggctgatcat ggccagcgcc attgaggagt ggaacctgca	540
ccggcgaatc gccctcaaga tcttgatgct tgttgaggtc cagccggcca ggctcatcct	600
ggggatgatg gtgaccacct cgttcttgct catgtggctg agcaacaccg cctccactgc	660
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aaaggacccc agccaggaga gtgaagagaa cacaggaata gaaccaata ctttctctc	780
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tatccatgaa accatagggt ttgtgtgcta gttctagttt ttaaaatatg aattaaatta	1080
aatacgtatc tgttaaaact taaaaaaaaa aaaaaaaaaa ctcgag	1126

<210> 61

<211> 2078

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (337)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (492)

<223> n equals a,t,g, or c

<400> 61

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gtgataatgc tttgtgcatg ttttctatta tttagaaaat gaaaacagca gtcatttgac	120
cagccatggt atgacaccag ataataattct gcaaggatct tccaaacagg gagaaactgc	180
aatgggaaca atctttggat atctacattg tgtcaaatgt tatgtgcttt atttcatttt	240
catacttata acagctgtat atcacagttt ttattatcca cattatagag gcaaggcact	300
gatatcagga acttgagtaa ttggcttaca cagcaantgt agttgaaata gaagccagga	360
ctgtctgatt cccaagacag tgttcttgta ctgcaggtaa gcctgggtgt gctgggkttc	420
cctagcactg agtattgcag aaatacggag atttatttac tcagggtgaat gatgaagcag	480
aatctttatt tngcttttta aattatkgat gggkckkgag ttaagctagt tcaccaatga	540
gtctcaaagg gtgaagaact ggcctgtgta gttttaaacc aaagcagcag ttttcttcat	600
ttgtagatat tatatttaat ttaccttgca tttccaatag cattaaatat tagaagcgta	660
taagcttttt ctttttatgc ctaggggata tggcttaaca ctgagaaaca cttgagaaac	720
actgccacat tctaaggaac aaccaataat aagaaaaatt atttcatata aaaggatgca	780

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tttttcttta	aagggtgtgt	tttcaaaaca	tgatgttatt	tcatatacmt	atataatatat	1020
atgcacacat	acataacmt	catgcatgka	tcatatatgt	gtgtgtatgt	atgtatctat	1080
cttcaatctt	tcaggaaagt	ttgtaaaawa	tagccctaag	tagaattatg	gggaaacagt	1140
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tgtagtccca	gctactgggg	aggctgaggc	aggagaatgg	cgtgaacctg	ggaggcggaa	1980
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<210> 62
 <211> 762
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (10)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (12)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (42)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (219)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (747)
 <223> n equals a,t,g, or c

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ggccagtgag	
cgcaacgcaa	ttaatgtgag
ttagctcact	cattaggcac
cccaggcttt	acactttatg
cttccggctc	gtatgttgtg
tgggaattgtg	agcggatanc
aatttcacac	aggaaacagc
	240

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<210> 63

<211> 1094

<212> DNA

<213> Homo sapiens

<400> 63

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tgttccatgt atgataacgg tgactggggg gtttacagag agaggcatac aaatagtgtt	1020
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agggggggcc cggt	1094

<210> 64

<211> 1361

<212> DNA

<213> Homo sapiens

<400> 64

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ttgtgtatcc tgtgatttt ctgtgtagtt ggtctatcag ttgttgggag aagagtgttg	180
aagtctacaa ctataattgt gtatttgtct attactcctt tcagttcctt cagttccatt	240
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ccctgggctc aaacgacctg cccagctcag cctcccagag aaatatgatt ttaattagca	840
catttagatc atttactttc aatggaatta ttgatgtatt acaattcaag tctgtcattt	900

tatttattgc	cttccatttt	tccctccggt	tttcatttct	gtgctttttt	tctttgcatg	960
taaacatggt	ttaggattct	gttttgatgt	atttagagta	tttttttagt	tatcgggtta	1020
tgtagctttt	ctagtggatc	ctttaagtat	tacattatat	atacataact	aagaagtata	1080
tcagtgtcat	cattttacca	gttcaagtaa	agtacagaaa	tctttgtccc	ttttacctgt	1140
cctgcttata	atgtaaagt	cttaaagatt	tccttgacac	acatttagaa	ccatatcaca	1200
gtgttgtttt	tgtttcagtt	gtgaaatata	atttagaaac	tcatgagaat	aaaaacccat	1260
tatatatttt	tataaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1320
aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aggcgggcgc	c		1361

<210> 65
 <211> 947
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (67)
 <223> n equals a,t,g, or c

<400> 65	
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acgcgtncgg	tttctgggtt
ctgaaggctc	accctagaaa
tccttacaca	tacaggaaga
gctctccctg	tcttcatttc
cctcagtact	tartctacag
tcagctctcc	ctgctctcca
tttaccctcc	agggcatctgt
ggcatagggg	gcaagctctt
attagatcca	cctggagcac
tgggtcacca	gttcccacct
tcccagagact	ctctctgact
tccacagatt	tgggtggctg
gtccccccca	gtcactttct
ctacagctgc	attaaaatca
aggatccaag	cttacgtacg
	ctgcatgcg
	acatcaagct
	ctgaaga
	60
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	360
	420
	480
	540
	600
	660
	720
	780
	840
	900
	947

<210> 66
 <211> 1376
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (18)
 <223> n equals a,t,g, or c

<400> 66	
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gcgcgggcgc	cctgcggtgt
cggcgctgcc	gcgggggctt
atagtgcagg	gagggacaga
ggcatgcatg	ttatcatagc
ataaaagaag	aaaccttgaa
acttccatcc	ggcagtttgt
atcaacaatg	ctggggtgat
catttcggcc	tgaactacct
	agggcacttc
	ctgctgacca
	accttctctt
	ggatacgtg
	60
	120
	180
	240
	300
	360
	420
	480
	540

aaagagtctg ggtcccttg ccacagtgcg aggggtggta cegtctctc tgccacccat	600
tacgtcgctg agctgaacat ggatgacctt cagagcagt cctgctactc accccacgca	660
gcctacgccc agagcaagct ggcccttgct ctgttcacct accacctcca gcggtgctg	720
gcggctgagg gaagccacgt gaccgccaac gtgggtggacc cgggggtgg caacacggac	780
stctacaagc acgtgttctg ggccaccctg ctggcgaaga agcttctcgg ctgggtgctt	840
ttcaagacct ccgatgaagg agcgtggact tccatctacg cagcagtcac ccagagctg	900
gaaggagttg gtggccgtta cctatacaac gagaaagaga ccaagtccct ccacgtcacc	960
tacaaccaga aactgcagca gcagctgtgg tctaagagtt gtgagatgac tggggtcctt	1020
gatgtgacct tgtgatatac tgtctcagga tagctgctgc cccaagaaac acattgcacc	1080
tgccaatagc ttgtgggtct gtgaagactg cgggtgttga gtttctcaca cccacctsc	1140
cacagggctc tgcctcttag ttttgagaca gctgcctcaa cctctgcaga acttcaagaa	1200
gccaaataaa catthttggag gataatcacc ccaagtggc ttcaaccata aactttgtga	1260
ttccaaagtg cccagttgtc acaggtgcca taaataatta cattttccaa cataaaaaaa	1320
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaagggc ggccgc	1376

<210> 67

<211> 2434

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (10)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (12)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (27)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (73)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (75)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (103)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (130)

<223> n equals a,t,g, or c

<400> 67

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cgtgttttct ttntncgagt agtgtgctgt gtaactaaa ttngccggtt cgctttccat	120

ttcctgacan	ttgagatgga	atgccttgac	cattggtgct	ctgacagaga	agtcattggag	180
tcattgccat	ttcctgggtg	cccttttggg	atgtgatccct	gttagtagag	gttttctagc	240
ttctactaag	atattttctt	ccctaaccat	catacacttg	gcattgttca	ttcccatctc	300
ctttcccctc	accttaaagg	agactacccc	tttgccccat	attgtcaacc	taattttctc	360
tcgtactctc	tctagtgaat	gatgtgctac	caagtatatg	ccaggctgtg	agaggattat	420
actgagtagt	agaaagaagc	taatttgaaa	taaaaattat	ttgtataatt	aagaaagcag	480
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cataaagatg	atagcatgtc	aatatattag	cctagccatt	atgttagcct	ttgttaggtg	600
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gaggaagggt	ttcatatatg	atctatcttt	ggattaaaaa	gaacatttat	gaaatcaagc	780
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aataaagtcc	ttttctctta	caggtattaa	atgaggacag	agaacctcag	gtgttcttat	960
gctagtgtct	gctgagtgtc	tactaagaaa	gcaattccaa	atagatgtat	acatctagag	1020
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tcccataaat	tattggaata	taatcccata	aattatcacc	ttttatgact	ggaaaatatt	1140
tgccaatgaa	gaaatgggtc	gtaggtattt	gtcttaagat	ttttggctgt	ttaataaaaa	1200
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tatcatgtgc	ctttgaaatt	tgacagctga	tttgggtgtt	ggatttctgc	ccagccattt	1320
atcagtatta	tcatttttatt	cagtagctgg	caggtgtatt	agacaaacga	gacttaggta	1380
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gcactatgtc	taggaggcaa	tatcctttta	aacagtgtct	tggctaagat	agatacttgt	1920
gaatcaaaga	tagcacagaa	atgaactaag	tatatcccat	ttggaattat	attttgatac	1980
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aaaaatgttt	tatatttttt	tttaagtaaa	atggacccag	taagaaaatt	aaaaatacca	2340
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aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaa			2434

<210> 68
 <211> 1086
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (10)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (77)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1056)

<223> n equals a,t,g, or c

<400> 68

ttgaaacacn cttttgagca ttaggtccca gctccaccgc ggtggcgggc gctctagaac	60
tagtggatcc cccgggntgc akkaattcgg caccagcaac ctgtagtgag ttggctgtca	120
ctcagcagct ctggaaaatt acctgtctgc actgaatttc ctcatcagta aaatggaaat	180
gattatagta ctgaccttgt aggattattc taaaaatcag agaagttcat gcagcttaga	240
acagtgccag gcacatggca aatgctatgg catacttaag catcttcctc tgtgggtgct	300
cgtcatcacc atgtgattgt gccttgcttg tccctgtttc acttttcaga gggagaaaag	360
tggccaactt taagaatcaa aattctgatg ttacttcggg aaatgcatag agccagagag	420
acacaatttg acttagtatg atccacatca tcccctcagg ctgaatagtg gtggcatgca	480
catctatacc aaaatgtttt accttttttg tagaaggaaa atatttgtat cttctattcc	540
atatcttaga tctttataag agcacttaag ttcaacctcc taagaaactg ccaattttgt	600
tgatcatgat agtctgcaca gattttcgta ctatttagtg ktgggagtg cttagggacc	660
atcaacaaca ggsccctcct tttatccatg agactactga ggccttgagg gttatttgtc	720
catccatggc ggggtgcacrg ctagaggtta tctggtagt agcccaacta agattagaac	780
ccaggaattt tgatttaatc tcaaatgacc tcttttattt ctgcatccgg gaaggagaag	840
aggaaagtaa acgggaaatt catgttatct atggaaaagt tatcagtttg atgtttatta	900
aatgatttgt ttcaggagat tgtttacaac ttttatcttc ctagacaata attttctgta	960
agagtaaagt catgttcatt aaggtagtca tattaatgta ttcagtaasc tgtgaagaaa	1020
aatatatatc aatgttttcc aataaaatc agtgantacc tgaaaaaaaa aaaaaaaaaa	1080
aaaaaa	1086

<210> 69

<211> 1262

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (568)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (639)

<223> n equals a,t,g, or c

<400> 69

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ttactgatct acaaccggtt ttaagttagt tgcctgctta aaattttctc atgaattctc	180
attacatttt caaacaaaat ccaaagtttt taccatgacc ttgtggatat ctttctgacc	240
tcatttacta ctgttatctt ccttattcat tccattccac ccacagtggc cttcttgcaa	300
gtcagagaat gcaacaaata tgctcctgcc ttggggcatt tgcacttctg ttcttttggc	360
ctggtcactt caccctccaca ttctccattt tttatgactt tcttctata tttggatctc	420
tgttcaaatg tcaccctcctc aaaaggcctt caaaactacc ctatttataa tagcacctgc	480
cactgccatc tccataccca ttttcatttt tccatagcac ttatccctac ttggcattat	540
gttatatat tgtttatttg kttactgmct gtctccccc ctggactgta agctccatga	600
ctgtaagtac atagatgaat tacaatatga atcaatggng aawtatcctt gmcatatat	660
atttaattgat tttgmctcca ttttaagtaa aaaaaaaaaa ccattttttt cactcttcaa	720
agtgatatag tttaatcttc taaactacat ttttctcatt tcccgaattt attaaatcag	780
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acagttttgt tatttcttctc ttattttagg aaatgatttg cagctgagtg aatcaggaag	1080
tgacagtgat gactgaagaa atatytagct ataaataaaa atttatacag catgtataat	1140

ttatttttga ttaacaataa aaatttcctaa gactgagggga aatatgtctt aactttttgat	1200
gataaaagaa attaaatttg attcagaaat ttcaaaaaaa aaaaaaaaaa aagggcgggcc	1260
gc	1262

<210> 70
<211> 1642
<212> DNA
<213> Homo sapiens

<400> 70
ggcgcgctgc cgggactgc ctgggttgcg ctgccggcca cgtccccgcg cggggcctca 60
ggctccttcc tactgtccga gggccaccag gccgcccggg gcctgctgcg cccggatgcg 120
tctgttacta gagtggagag tctaccttcg tctcacatgt gccacaaagg atggcatggc 180
ccgggagtgcc cccaccacgt ggctttcacc ccctgcaaag ccagacttcg cccagcgaca 240
cagtgtcaag cccacagctc tccaaggagg aagatgggtc aggtggggag catcycctta 300
gcagcagcct ctgatccctt ggccaagcag gagggaacca ttagcagcct gaggagctgg 360
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tgtggaataa gttgataata aaacgtctga ggatgtaacc atggcagcag cttctcctgt 600
cacattgacc aaagggattc ggcagcccam ctcaactcta tggaagtcac aacagaggac 660
acaagcagga cagatgtgag tgaaccagca acttcaggag gtgcagctga tgggtgtgacc 720
tccattgctc ccacggctgt ggctccagt acgactgcgg cctccattac gactgcggcc 780
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agcagcccca tgagcactcg tccaagtctt tccaagcaca tgcccagtga caccgcggca 1140
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cagcctgtgg ttaacacaac awataaatcc acamccatgc cctcaaacac aaccmcwgag 1260
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taaaaaaaaa aaaaaaaaaa gg 1642

<210> 71
<211> 921
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (4)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (9)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (11)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (15)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (20)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (901)

<223> n equals a,t,g, or c

<400> 71

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agataagatt	aagggctggg	tctgtgctca	attaactcct	gtgggcacgg	gggctgggaa	180
gagcaaagtc	agcgggtgcct	acagtcagca	ccatgctggg	cctgccgtgg	aagggaggtc	240
tgctcctggg	gctgctgctg	cttctcttag	gctcccagat	cctgctgac	tatgcctggc	300
atttccacga	gcaaagggac	tgtgatgaac	acaatgtcat	ggctcgttac	ctccctgcca	360
cagtggagtt	tgctgtccac	acattcaacc	aacagagcaa	ggactactat	gcctacagac	420
tggggcacat	cttgaattcc	tggaaggagc	aggtggagtc	caagactgta	ttctcaatgg	480
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tccaagaaa	cacagagctg	aacaatactt	tcacctgctt	cttcaccatc	agcaccaggc	600
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tgtttgagat	ctcagatcag	tgtttttagaa	aatccacaca	tcttgagcct	aatcatgtag	840
tgtagatcat	taaacatcag	catttttaaga	aaaaaaaaaa	aaaaaaaarct	cgagggggggg	900
nccggtaccc	agggcggaag	a				921

<210> 72

<211> 906

<212> DNA

<213> Homo. sapiens

<220>

<221> SITE

<222> (34)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (833)

<223> n equals a,t,g, or c

<400> 72

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gggggaatgg	ttcgtcctgg	gcctggcggg	caacagcttc	aggccggagc	acagggcgct	360
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tgcgatgact	cgaggccagc	actgtgacac	atgggtcttat	gtgctgatac	cggcagccca	480
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agattg						906

<210> 73
 <211> 680
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (7)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (9)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (15)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (16)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (22)
 <223> n equals a,t,g, or c

<400> 73	
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cnagctccac	cgcggtggcg
gcccgtctag	aactagtggg
60	
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gaccctagaa	aagccaccac
120	
gacctgtggg	ccatgatgct
acccaatgg	ctgctgctgc
tggtccttct	cttcttcttt
180	
ctcttctctc	tcaccagggg
ctcactttct	ccaacaaaat
acaacctttt	ggagctcaag
240	
gagctttgca	tccggaacca
ggactgcgag	actggctgct
gccaacgtgc	tccagacaat
300	
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gaaggggtcc	gagggcagtc
tgtgtcaaac	gcaggtgttc
360	
tttggccagt	atagagcgtg
tccctgcctg	cggaacctga
cttgtatata	ttcaaagaat
420	
gagaaatggc	ttagcatcgc
ctatggccgt	tgtcagaaaa
ttggaaggca	gaagtgtgct
480	
aagaaaatgt	tcttctagt
ctccctcctt	cttgtgscet
cctcctycty	cacctgctct
540	
cctccctacc	cagagctctg
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gcctccacca	tgagtggagg
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<210> 74
 <211> 1633
 <212> DNA

<213> Homo sapiens

<400> 74

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<210> 75

<211> 1022

<212> DNA

<213> Homo sapiens

<400> 75

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cg						1022

<210> 76
 <211> 1184
 <212> DNA
 <213> Homo sapiens

<400> 76
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 aagtatatgg tggacagaca atgccaatt gcctttcaga gactgtggcc ctgtgcaccc 420
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<210> 77
 <211> 312
 <212> DNA
 <213> Homo sapiens

<400> 77
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 ggtgcatttt gtgtgtgcct tccagagcca gtggactggt gtgtatccaa tgatgccacc 180
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 agggcgcccg ct 312

<210> 78
 <211> 1370
 <212> DNA
 <213> Homo sapiens

<400> 78
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<210> 79
 <211> 368
 <212> DNA
 <213> Homo sapiens

<220>
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 <223> n equals a,t,g, or c

<220>
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<220>
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<220>
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 <223> n equals a,t,g, or c

<220>
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 <222> (367)
 <223> n equals a,t,g, or c

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<210> 80
 <211> 1088
 <212> DNA
 <213> Homo sapiens

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 <223> n equals a,t,g, or c

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<220>
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<220>
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 <222> (11)
 <223> n equals a,t,g, or c

<400> 80
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 aattggttca tcttgggaaa ggaaggccta ggaagctgat gacctacttg ttttgttcat 180
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 aaactcaatc tcaactctctc aaagctttct ggccaggttt tcctcacaca cccatagaaa 1020
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 aagatttg 1088

<210> 81
 <211> 1862
 <212> DNA
 <213> Homo sapiens

<400> 81
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 agtcaacctt tctttagggc ccagaggaaa acctatcacc ttctacacct tcccagatgc 180
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 agcactggtc ccagcctatg ccattgtgtg tcaccttggc tcctgtctcc tactggctgt 300
 agatcttttg gargggagga actgggggaat tttcatcctg gggctatggg atagtgttta 360

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ctagcctggg	ccatagaatg	agactccttc	tcaaaaaaaa	aaaagaaaaa	aaaaaactcg	1860
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<210> 82

<211> 1618

<212> DNA

<213> Homo sapiens

<400> 82

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<210> 83
<211> 2034
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>
<221> SITE
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<223> n equals a,t,g, or c

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<221> SITE
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<400> 83
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<210> 84

<211> 2240

<212> DNA

<213> Homo sapiens

<400> 84

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<210> 85

<211> 1488

<212> DNA

<213> Homo sapiens

<400> 85

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<210> 86

<211> 3174

<212> DNA

<213> Homo sapiens

<400> 86

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<210> 87

<211> 2780

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (2760)

<223> n equals a,t,g, or c

<400> 87

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<210> 88

<211> 1061

<212> DNA

<213> Homo sapiens.

<400> 88

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<210> 89

<211> 1342

<212> DNA

<213> Homo sapiens

<400> 89

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<211> 770

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (690)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (762)

<223> n equals a,t,g, or c

<400> 90

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 <212> DNA
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 <211> 2950
 <212> DNA
 <213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<210> 96

<211> 2683

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (2640)

<223> n equals a,t,g, or c

<220>

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<213> Homo sapiens

<220>
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<222> (5)
<223> n equals a,t,g, or c

<400> 97

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<210> 98

<211> 1957

<212> DNA

<213> Homo sapiens

<400> 98

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<210> 99

<211> 1112

<212> DNA

<213> Homo sapiens

<400> 99

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<210> 100

<211> 887

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (303)

<223> n equals a,t,g, or c

<400> 100

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<210> 101

<211> 1248

<212> DNA

<213> Homo sapiens

<400> 101

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<210> 102

<211> 1841

<212> DNA

<213> Homo sapiens

<400> 102

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<210> 103
 <211> 685
 <212> DNA
 <213> Homo sapiens

<220>
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 <222> (678)
 <223> n equals a,t,g, or c

<220>
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 <222> (679)
 <223> n equals a,t,g, or c

<400> 103						
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taattacatt	gtctgattta	gaatgtgatt	acattaatgc	tagatcatgt	tgctcaaaat	180
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tgtcattgca	ctgggttcac	ttccttctca	acttacctgt	tgccacttgg	aatatatata	300
gatacattat	ggtgccgagt	ggtaacatgg	gagtgtttga	tccaacagaa	atacacaatc	360
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gcttcttcat	gtatctttat	agtatgatct	tagctttgat	aaatgactga	agctggagaa	480
gccgtgtgtg	aagtcagcct	acactacagt	gcacagttga	ggagccagag	acttcttaaa	540
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aaaaaaaaaa	aaaaaanna	aaaaa				685

<210> 104
 <211> 1168
 <212> DNA

<213> Homo sapiens

<400> 104

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cctggccctc	tcgctgttgc	tggtctctgg	ctccctcctc	ccagggccag	gcgccgctca	180
gaacgtgaga	gtacaatctg	gacaggatca	gaagtagaga	atgaagttgt	aagagaaagg	240
gaaagacaga	agaaaggctg	cagtagtaca	aggagaaaag	caggatgcaa	gaatgaggaa	300
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agggacctct	aaagtaaatt	cacacatcaa	agttaaaata	atgttggaga	atcacctcct	420
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gttacatatt	ttaggcttat	atacataaca	aaactttctaa	ctgaatttaa	aagtgatctt	720
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cagatacctg	ctgttttctt	gttgtgtttc	ttgtttttca	aataaataaa	ctgagtgtta	1140
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<210> 105

<211> 1175

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (24)

<223> n equals a,t,g, or c

<400> 105

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aaaatgcctt	cacatatacg	agctcattta	ttctctcttc	tcttctttct	attcatctat	240
caaggaatat	cttctataag	ccaggcatca	ggcttgacac	tgaagacaca	aaatgaaaaa	300
gatatacaag	tctctattct	taaagagttc	gtagtttaat	gaagtgaccc	aaaaagtaaa	360
cagttgcaat	ataacatgca	aaggagtgtg	atgaaatata	cctagagtac	tatgaaaatg	420
gcatagaggg	accaagcctg	taatgaagtc	agagaaaagta	aaagaggtga	agcckgagct	480
aagtttttaa	ggatgaacaa	aaattgacca	gacaaaggag	ttggagaagt	gggatggtag	540
aggataaaag	ccttttcta	ttggggaagt	gtgagtcgtc	gatattagat	gatattatta	600
atagattgtg	cacagagtgc	acatggtaga	gaggtgagag	atgaggtagc	actgttaggg	660
cagataggtg	aattctcaca	gtaaccctgt	gwtgtacmtt	atcatcctcc	tctccattat	720
gtagggggaga	acaccaaagc	ccaaagagat	taagtaactt	tccagaattt	tgatttcaaa	780
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<210> 106

<211> 1021

<212> DNA

<213> Homo sapiens

<400> 106

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ggatgtgcat ttaccaatca gaacagatgt tggctttact gcttgtatta gttttctgta    180
ttagtttgct tgtattagtt tgctggggca gccataacaa agtaccacag aaatttatat    240
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aaggactctc ttgttggcct gtagatgggt gttgtctccc tgtgtcttca cctgcacttc    360
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cattatactt tttcctttgt gtgtttggaa atttttataa taagcaggaa aaataaaagt    960
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<210> 107

<211> 830

<212> DNA

<213> Homo sapiens

<400> 107

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cctctgactg taaaaagaag tagcagttcc gaaagcaaga gttccctatg aacacggaag    180
aagacattgg caacttttga gtacaacaac tatatttaat agagtaattt aagaacatca    240
gccagtgaat tttatacaag atagtgaag agaaaaggaa gattaattag gggtagttta    300
ggatgccatt aaatagccta gaattagggg agtagtcgtt gaatagaaag gaggccacaa    360
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aggataatga ggaacaaaat agagaactca gaagcaatat ctgactgtta tcatgggaag    480
aatttttttg cttgcttgag gctggatatt gaagtggatc aggatacttg agtgactatc    540
tgatgggctt ttggaactag ctctcaagag gtgaaaatta gctttttttt ctttttcttt    600
cttttttttt ttttttgagg caaggctca ctgttggtga ggctgaacct cctgggctca    660
agcagttgtc ccattgcagc ctctcagat actctgtaag ccaaggcagg gggaatattt    720
tgtgtcagat agtttgaggc tgtgtgagc taagatcaca ctgctgtgct cacttcagcc    780
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<210> 108

<211> 1301

<212> DNA

<213> Homo sapiens

<400> 108

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cagtgcctcg attcatcaag tacacaggct atgggaatgc tgctggcctt ctggctgcca    180
ggggcctcat ggcaggaggc cggcccaggg gccagtactc agaggatgag gacacagaca    240
cagatgagta caaggaagcc aaagccagca taaaccctgt gaccgggagg gtggaggaga    300
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tggtgaccat	gtttgacaag	ctctccagga	acagagtcac	ccagccaatg	gggatgagtc	420
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gagatttata	ccacatacca	cacatagcca	cagaaacatc	atcttgaaat	aaagaagagt	1260
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<210> 109

<211> 1932

<212> DNA

<213> Homo sapiens

<400> 109

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ttaggcacca	taatcagtat	gagccaacaa	tattttaaact	tgattcaggc	cacattcaga	180
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catgtaagct	aaatggaacc	agcaatggtg	ctcaagtttt	tatcatccct	tccagaaaat	360
ctttttctac	catctcttct	attttttgcc	tggctttgct	ggaacatggg	ttgtggttct	420
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<210> 110
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 <212> DNA
 <213> Homo sapiens

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 <223> n equals a,t,g, or c

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<210> 111
 <211> 2871
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1234)
 <223> n equals a,t,g, or c

<220>
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 <223> n equals a,t,g, or c

<220>
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 <223> n equals a,t,g, or c

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<220>
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 <223> n equals a,t,g, or c

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 <212> DNA
 <213> Homo sapiens

<400> 114

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<210> 115
 <211> 1286
 <212> DNA
 <213> Homo sapiens

<220>
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 <222> (1149)
 <223> n equals a,t,g, or c

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 <211> 2189
 <212> DNA
 <213> Homo sapiens

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<211> 1763

<212> DNA

<213> Homo sapiens

<400> 117

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<210> 118
 <211> 1375
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (18)
 <223> n equals a,t,g, or c

<400> 118
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 atagtgcagg gagggacaga tggcattggc tattctacag cgaacatctg gcgagacttg 240
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 taaaagaaga aaccttgaac gacaaagtgg aatttttata ctgtgacttg gcttccatga 360
 cttccatccg gcagtttgtg cagaagttca agatgaagaa gattcctctc catgtcctga 420
 tcaacaatgc tgggggtgat atggtccttc agaggaaaac cagagatgga ttcgaagaac 480
 atttcggcct gaactacctt gggcaacttc tgctgaccaa ccttctcttg gatacgtgta 540
 aagagtcttg gtcccctggc cacagtgcga ggggtggcac cgtctcctct gccacccatt 600
 acgtcgctga gctgaacatg gatgaccttc agagcagtg cgtctactca cccacgcag 660
 cctacgcccc gagcaagctg gcccttgctc tgttcacctt ccacctccag cggtgtgctg 720
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 aaggagtgg tggccgttac ctatacaac agaaagagac caagtcctc cacgtcacct 960
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 ccaaataaac attttgagg ataataccc caagtggctt tcaaccataa actttgtgat 1260
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 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaggcgc gccgc 1375

<210> 119
 <211> 1022
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (937)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (990)
 <223> n equals a,t,g, or c

<400> 119
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 gcccccggt ctacaaaatc tacggggaga gggactctga aaggggcccc gccagcgtcc 120
 ctgagacgcc aacggcagtc actgcccccc attccagctc ctgggatacg tactatcagc 180

cccgtgccct	ggagaaacat	gctgacagca	tccctggcact	ggcttcagta	ttctgggtcca	240
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tgtccaaagt	gggtgccgttt	tctcactatg	ctgggacatt	gctgctactt	ctggcaggtg	360
tggcctgctc	cgaggcattg	gccgctggac	caacccccag	taccggcagt	tcataccat	420
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gg						1022

<210> 120

<211> 2311

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (654)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2293)

<223> n equals a,t,g, or c

<400> 120

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<210> 121
 <211> 1286
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1284)
 <223> n equals a,t,g, or c

<400> 121	
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cctgggatcc	caggtcgga
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ttattcattt	tgcttcaatc
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<210> 122
 <211> 1380
 <212> DNA
 <213> Homo sapiens

<400> 122	
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<210> 123
 <211> 3793
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1102)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1132)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1199)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1228)
 <223> n equals a,t,g, or c

<220>
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 <222> (1229)
 <223> n equals a,t,g, or c

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 <222> (1231)
 <223> n equals a,t,g, or c

<220>
 <221> SITE

<222> (3176)

<223> n equals a,t,g, or c

<400> 123

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taggttcaag	actatctgtt	taaatattac	tgaaaaacaa	agtaagacag	tactatgctt	3120
acctcttaac	ttgataatgt	caaaccaggc	atgttaaatg	acatcataga	aaaganttca	3180
agataattta	tagaagttaa	atttatattg	acagaaaata	attgtatgaa	aatctctact	3240
atggggctgg	aacatggttg	aacattagaa	tgatataaaa	aattatata	attctccaaa	3300

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tccacgctag	acctgtcaaa	ttagagaatc	tagagattag	acctggcgtg	tcagcaaggt	3360
catccaggaa	gcagaggctg	agacggagtt	aggtgtgatt	acttacatag	tcgattacat	3420
tttacaaata	acattttata	tgtctcattt	actgtgcttt	ctcccatcc	cattttgtat	3480
cttttccttt	gctttgctag	atttgtcaat	tttctctctc	tttctgtctc	tctctctttc	3540
aatatctcta	ataatttgaa	agtaattcat	cataactaaa	tatctattgg	ggttatgctt	3600
cacttacaaa	cttctgaaaa	cggctttact	gagatataat	tgatatattt	aagtgtacag	3660
tttggttaaat	tttgcacata	tttaaaatgt	ggactttggt	aaatgttgac	atagttttac	3720
atctgtgaaa	ccatcagcat	aatcaagata	ataaacttgt	ccatcacccc	ccaaaaaaa	3780
aaaaaaaaaa	aaa					3793

<210> 124

<211> 370

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (370)

<223> Xaa equals stop translation

<400> 124

Met	Leu	Gly	Ala	Phe	Val	Trp	Pro	Ser	Leu	Leu	Leu	Leu	Ala	Ala	Ala
1				5					10					15	

Cys	Ile	Cys	Leu	Leu	Thr	Phe	Ile	Asn	Cys	Ala	Tyr	Val	Lys	Trp	Gly
			20					25					30		

Thr	Leu	Val	Gln	Asp	Ile	Phe	Thr	Tyr	Ala	Lys	Val	Leu	Ala	Leu	Ile
		35					40					45			

Ala	Val	Ile	Val	Ala	Gly	Ile	Val	Arg	Leu	Gly	Gln	Gly	Ala	Ser	Thr
	50					55					60				

His	Phe	Glu	Asn	Ser	Phe	Glu	Gly	Ser	Ser	Phe	Ala	Val	Gly	Asp	Ile
65					70					75				80	

Ala	Leu	Ala	Leu	Tyr	Ser	Ala	Leu	Phe	Ser	Tyr	Ser	Gly	Trp	Asp	Thr
			85					90						95	

Leu	Asn	Tyr	Val	Thr	Glu	Glu	Ile	Lys	Asn	Pro	Glu	Arg	Asn	Leu	Pro
		100						105					110		

Leu	Ser	Ile	Gly	Ile	Ser	Met	Pro	Ile	Val	Thr	Ile	Ile	Tyr	Ile	Leu
	115						120					125			

Thr	Asn	Val	Ala	Tyr	Tyr	Thr	Val	Leu	Asp	Met	Arg	Asp	Ile	Leu	Ala
	130					135						140			

Ser	Asp	Ala	Val	Ala	Val	Thr	Phe	Ala	Asp	Gln	Ile	Phe	Gly	Ile	Phe
145				150						155				160	

Asn	Trp	Ile	Ile	Pro	Leu	Ser	Val	Ala	Leu	Ser	Cys	Phe	Gly	Gly	Leu
			165						170					175	

Asn	Ala	Ser	Ile	Val	Ala	Ala	Ser	Arg	Leu	Phe	Phe	Val	Gly	Ser	Arg
			180					185					190		

Glu	Gly	His	Leu	Pro	Asp	Ala	Ile	Cys	Met	Ile	His	Val	Glu	Arg	Phe
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

195	200	205
Thr Pro Val Pro Ser Leu Leu Phe Asn Gly Ile Met Ala Leu Ile Tyr		
210	215	220
Leu Cys Val Glu Asp Ile Phe Gln Leu Ile Asn Tyr Tyr Ser Phe Ser		
225	230	235 240
Tyr Trp Phe Phe Val Gly Leu Ser Ile Val Gly Gln Leu Tyr Leu Arg		
	245	250 255
Trp Lys Glu Pro Asp Arg Pro Arg Pro Leu Lys Leu Ser Val Phe Phe		
	260	265 270
Pro Ile Val Phe Cys Leu Cys Thr Ile Phe Leu Val Ala Val Pro Leu		
	275	280 285
Tyr Ser Asp Thr Ile Asn Ser Leu Ile Gly Ile Ala Ile Ala Leu Ser		
	290	295 300
Gly Leu Pro Phe Tyr Phe Leu Ile Ile Arg Val Pro Glu His Lys Arg		
	310	315 320
Pro Leu Tyr Leu Arg Arg Ser Trp Gly Leu Pro Gln Gly Thr Ser Arg		
	325	330 335
Ser Cys Val Cys Gln Leu Leu Gln Lys Trp Ile Trp Lys Met Glu Glu		
	340	345 350
Arg Cys Pro Ser Asn Gly Ile Pro Ser Leu Thr Lys His His Leu Glu		
	355	360 365
Ser Xaa		
370		

<210> 125
 <211> 86
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (86)
 <223> Xaa equals stop translation

<400> 125
Met Gly Phe Trp Cys Gly Cys Pro Phe Cys Leu Leu Val Val Leu Leu
1 5 10 15
Thr Asp Arg Thr Leu Ser Cys Arg Ser Val Gly Val Pro Cys Asn Val
20 25 30
Arg Cys Gln Cys Ala Pro Ala Gly Gly Cys Leu Pro Val Arg Leu Leu
35 40 45
Ala Gly Gln Gly Ser Gly Thr His Leu Arg Arg Gln Ser Ala Arg Ser
50 55 60

Gln Ile Ser Ser Cys Met Leu Gly Glu Pro Leu Leu Ser Ser Lys Leu
 65 70 75 80

Ser Asp Arg Asp Ile Xaa
 85

<210> 126
 <211> 44
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (44)
 <223> Xaa equals stop translation

<400> 126
 Met Tyr Thr Lys Thr His Lys Phe Lys Phe Tyr Asn Phe Leu Ser Leu
 1 5 10 15

Trp Ile Trp Lys Ile Phe Phe Leu Leu Phe Phe Ile Leu Ile Val Ala
 20 25 30

Leu Ala Phe Pro Ile Pro Cys Leu Ser Ile Phe Xaa
 35 40

<210> 127
 <211> 319
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (264)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (303)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 127
 Met Asn Thr Asp His Leu Arg Leu Thr Val Pro Asn Gly Ile Gly Ala
 1 5 10 15

Leu Lys Leu Arg Glu Met Glu His Tyr Phe Ser Gln Gly Leu Ser Val
 20 25 30

Gln Leu Phe Asn Asp Gly Ser Lys Gly Lys Leu Asn His Leu Cys Gly
 35 40 45

Ala Asp Phe Val Lys Ser His Gln Lys Pro Pro Gln Gly Met Glu Ile
 50 55 60

Lys Ser Asn Glu Arg Cys Ser Phe Asp Gly Asp Ala Asp Arg Ile
 65 70 75 80

Val Tyr Tyr Tyr His Asp Ala Asp Gly His Phe His Leu Ile Asp Gly
 85 90 95
 Asp Lys Ile Ala Thr Leu Ile Ser Ser Phe Leu Lys Glu Leu Leu Val
 100 105 110
 Glu Ile Gly Glu Ser Leu Asn Ile Gly Val Val Gln Thr Ala Tyr Ala
 115 120 125
 Asn Gly Ser Ser Thr Arg Tyr Leu Glu Glu Val Met Lys Val Pro Val
 130 135 140
 Tyr Cys Thr Lys Thr Gly Val Lys His Leu His His Lys Ala Gln Glu
 145 150 155 160
 Phe Asp Ile Gly Val Tyr Phe Glu Ala Asn Gly His Gly Thr Ala Leu
 165 170 175
 Phe Ser Thr Ala Val Glu Met Lys Ile Lys Gln Ser Ala Glu Gln Leu
 180 185 190
 Glu Asp Lys Lys Arg Lys Ala Ala Lys Met Leu Glu Asn Ile Ile Asp
 195 200 205
 Leu Phe Asn Gln Ala Ala Gly Asp Ala Ile Ser Asp Met Leu Val Ile
 210 215 220
 Glu Ala Ile Leu Ala Leu Lys Gly Leu Thr Val Gln Gln Trp Asp Ala
 225 230 235 240
 Leu Tyr Thr Asp Leu Pro Asn Arg Gln Leu Lys Val Gln Val Ala Asp
 245 250 255
 Arg Arg Val Ile Ser Thr Thr Xaa Ala Glu Arg Gln Ala Val Thr Pro
 260 265 270
 Pro Gly Leu Gln Glu Ala Ile Asn Asp Leu Val Lys Lys Tyr Lys Leu
 275 280 285
 Ser Arg Ala Phe Val Arg Pro Ser Gly Thr Glu Asp Val Val Xaa Ser
 290 295 300
 Ile Cys Arg Ser Arg Leu Thr Arg Lys Cys Arg Ser Pro Cys Thr
 305 310 315

<210> 128

<211> 46

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (46)

<223> Xaa equals stop translation

<400> 128

Met Asp Met Val Cys Phe Cys Ile Tyr Leu Gly Leu Leu Lys Phe Ile
 1 5 10 15

Ser Ala Ile Phe Cys Ser Phe Ser Glu Glu Val Leu Tyr Ile Ser Phe
20 25 30

Val Lys Cys Ile Pro Lys Tyr Phe Val Glu Met Leu Leu Xaa
35 40 45

<210> 129

<211> 709

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (189)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (275)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (414)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (438)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (641)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (643)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (696)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (697)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 129

Met Ala Gly Leu Asn Cys Gly Val Ser Ile Ala Leu Leu Gly Val Leu
1 5 10 15

Leu Leu Gly Ala Ala Arg Leu Pro Arg Gly Ala Glu Ala Phe Glu Ile
20 25 30

Ala Leu Pro Arg Glu Ser Asn Ile Thr Val Leu Ile Lys Leu Gly Thr
 35 40 45
 Pro Thr Leu Leu Ala Lys Pro Cys Tyr Ile Val Ile Ser Lys Arg His
 50 55 60
 Ile Thr Met Leu Ser Ile Lys Ser Gly Glu Arg Ile Val Phe Thr Phe
 65 70 75 80
 Ser Cys Gln Ser Pro Glu Asn His Phe Val Ile Glu Ile Gln Lys Asn
 85 90 95
 Ile Asp Cys Met Ser Gly Pro Cys Pro Phe Gly Glu Val Gln Leu Gln
 100 105 110
 Pro Ser Thr Ser Leu Leu Pro Thr Leu Asn Arg Thr Phe Ile Trp Asp
 115 120 125
 Val Lys Ala His Lys Ser Ile Gly Leu Glu Leu Gln Phe Ser Ile Pro
 130 135 140
 Arg Leu Arg Gln Ile Gly Pro Gly Glu Ser Cys Pro Asp Gly Val Thr
 145 150 155 160
 His Ser Ile Ser Gly Arg Ile Asp Ala Thr Val Val Arg Ile Gly Thr
 165 170 175
 Phe Cys Ser Asn Gly Thr Val Ser Arg Ile Lys Met Xaa Glu Gly Val
 180 185 190
 Lys Met Ala Leu His Leu Pro Trp Phe His Pro Arg Asn Val Ser Gly
 195 200 205
 Phe Ser Ile Ala Asn Arg Ser Ser Ile Lys Arg Leu Cys Ile Ile Glu
 210 215 220
 Ser Val Phe Glu Gly Glu Gly Ser Ala Thr Leu Met Ser Ala Asn Tyr
 225 230 235 240
 Pro Glu Gly Phe Pro Glu Asp Glu Leu Met Thr Trp Gln Phe Val Val
 245 250 255
 Pro Ala His Leu Arg Ala Ser Val Ser Phe Leu Asn Phe Asn Leu Ser
 260 265 270
 Asn Cys Xaa Arg Lys Glu Glu Arg Val Glu Tyr Tyr Ile Pro Gly Ser
 275 280 285
 Thr Thr Asn Pro Glu Val Phe Lys Leu Glu Asp Lys Gln Pro Gly Asn
 290 295 300
 Met Ala Gly Asn Phe Asn Leu Ser Leu Gln Gly Cys Asp Gln Asp Ala
 305 310 315 320
 Gln Ser Pro Gly Ile Leu Arg Leu Gln Phe Gln Val Leu Val Gln His
 325 330 335
 Pro Gln Asn Glu Ser Asn Lys Ile Tyr Val Val Asp Leu Ser Asn Glu

340	345	350
Arg Ala Met Ser Leu Thr Ile Glu Pro Arg Pro Val Lys Gln Ser Arg 355 360 365		
Lys Phe Val Pro Gly Cys Phe Val Cys Leu Glu Ser Arg Thr Cys Ser 370 375 380		
Ser Asn Leu Thr Leu Thr Ser Gly Ser Lys His Lys Ile Ser Phe Leu 385 390 395 400		
Cys Asp Asp Leu Thr Arg Leu Trp Met Asn Val Glu Lys Xaa Ile Ser 405 410 415		
Cys Thr Asp His Arg Tyr Cys Gln Arg Lys Ser Tyr Ser Leu Gln Val 420 425 430		
Pro Ser Asp Ile Leu Xaa Leu Pro Val Glu Leu His Asp Phe Ser Trp 435 440 445		
Lys Leu Leu Val Pro Lys Asp Arg Leu Ser Leu Val Leu Val Pro Ala 450 455 460		
Gln Lys Leu Gln Gln His Thr His Glu Lys Pro Cys Asn Thr Ser Phe 465 470 475 480		
Ser Tyr Leu Val Ala Ser Ala Ile Pro Ser Gln Asp Leu Tyr Phe Gly 485 490 495		
Ser Phe Cys Pro Gly Gly Ser Ile Lys Gln Ile Gln Val Lys Gln Asn 500 505 510		
Ile Ser Val Thr Leu Arg Thr Phe Ala Pro Ser Phe Arg Gln Glu Ala 515 520 525		
Ser Arg Gln Gly Leu Thr Val Ser Phe Ile Pro Tyr Phe Lys Glu Glu 530 535 540		
Gly Val Phe Thr Val Thr Pro Asp Thr Lys Ser Lys Val Tyr Leu Arg 545 550 555 560		
Thr Pro Asn Trp Asp Arg Gly Leu Pro Ser Leu Thr Ser Val Ser Trp 565 570 575		
Asn Ile Ser Val Pro Arg Asp Gln Val Ala Cys Leu Thr Phe Phe Lys 580 585 590		
Glu Arg Ser Gly Val Val Cys Gln Thr Gly Arg Ala Phe Met Ile Ile 595 600 605		
Gln Glu Gln Arg Thr Arg Ala Glu Glu Ile Phe Ser Leu Asp Glu Asp 610 615 620		
Val Leu Pro Lys Pro Ser Phe His His His Ser Phe Trp Val Asn Ile 625 630 635 640		
Xaa Asn Xaa Ser Pro Thr Ser Gly Lys Gln Leu Asp Leu Leu Phe Ser 645 650 655		

Val Thr Leu Thr Pro Arg Thr Val Asp Leu Thr Val Ile Leu Ile Ala
660 665 670

Ala Val Gly Gly Gly Val Leu Leu Leu Ser Ala Leu Gly Leu Ile Ile
675 680 685

Cys Cys Val Lys Lys Lys Lys Xaa Xaa Thr Arg Gly Pro Ala Val Gly
690 695 700

Ile Tyr Asn Gly Asn
705

<210> 130

<211> 415

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (415)

<223> Xaa equals stop translation

<400> 130

Met Thr Lys Ala Arg Leu Phe Arg Leu Trp Leu Val Leu Gly Ser Val
1 5 10 15

Phe Met Ile Leu Leu Ile Ile Val Tyr Trp Asp Ser Ala Gly Ala Ala
20 25 30

His Phe Tyr Leu His Thr Ser Phe Ser Arg Pro His Thr Gly Pro Pro
35 40 45

Leu Pro Thr Pro Gly Pro Asp Arg Asp Arg Glu Leu Thr Ala Asp Ser
50 55 60

Asp Val Asp Glu Phe Leu Asp Lys Phe Leu Ser Ala Gly Val Lys Gln
65 70 75 80

Ser Asp Leu Pro Arg Lys Glu Thr Glu Gln Pro Pro Ala Pro Gly Ser
85 90 95

Met Glu Glu Asn Val Arg Gly Tyr Asp Trp Ser Pro Arg Asp Ala Arg
100 105 110

Arg Ser Pro Asp Gln Gly Arg Gln Gln Ala Glu Arg Arg Ser Val Leu
115 120 125

Arg Gly Phe Cys Ala Asn Ser Ser Leu Ala Phe Pro Thr Lys Glu Arg
130 135 140

Ala Phe Asp Asp Ile Pro Asn Ser Glu Leu Ser His Leu Ile Val Asp
145 150 155 160

Asp Arg His Gly Ala Ile Tyr Cys Tyr Val Pro Lys Val Ala Cys Thr
165 170 175

Asn Trp Lys Arg Val Met Ile Val Leu Ser Gly Ser Leu Leu His Arg
180 185 190

Gly Ala Pro Tyr Arg Asp Pro Leu Arg Ile Pro Arg Glu His Val His
 195 200 205
 Asn Ala Ser Ala His Leu Thr Phe Asn Lys Phe Trp Arg Arg Tyr Gly
 210 215 220
 Lys Leu Ser Arg His Leu Met Lys Val Lys Leu Lys Lys Tyr Thr Lys
 225 230 235 240
 Phe Leu Phe Val Arg Asp Pro Phe Val Arg Leu Ile Ser Ala Phe Arg
 245 250 255
 Ser Lys Phe Glu Leu Glu Asn Glu Glu Phe Tyr Arg Lys Phe Ala Val
 260 265 270
 Pro Met Leu Arg Leu Tyr Ala Asn His Thr Ser Leu Pro Ala Ser Ala
 275 280 285
 Arg Glu Ala Phe Arg Ala Gly Leu Lys Val Ser Phe Ala Asn Phe Ile
 290 295 300
 Gln Tyr Leu Leu Asp Pro His Thr Glu Lys Leu Ala Pro Phe Asn Glu
 305 310 315 320
 His Trp Arg Gln Val Tyr Arg Leu Cys His Pro Cys Gln Ile Asp Tyr
 325 330 335
 Asp Phe Val Gly Lys Leu Glu Thr Leu Asp Glu Asp Ala Ala Gln Leu
 340 345 350
 Leu Gln Leu Leu Gln Val Asp Arg Gln Leu Arg Phe Pro Pro Ser Tyr
 355 360 365
 Arg Asn Arg Thr Ala Ser Ser Trp Glu Glu Asp Trp Phe Ala Lys Ile
 370 375 380
 Pro Leu Ala Trp Arg Gln Gln Leu Tyr Lys Leu Tyr Glu Ala Asp Phe
 385 390 395 400
 Val Leu Phe Gly Tyr Pro Lys Pro Glu Asn Leu Leu Arg Asp Xaa
 405 410 415

<210> 131

<211> 242

<212> PRT

<213> Homo sapiens

<400> 131

Met Gln Leu Gly Ser Val Leu Leu Thr Arg Cys Pro Phe Trp Gly Cys
 1 5 10 15
 Phe Ser Gln Leu Met Leu Tyr Ala Glu Arg Ala Glu Ala Arg Arg Lys
 20 25 30
 Pro Asp Ile Pro Val Pro Tyr Leu Tyr Phe Asp Met Gly Ala Ala Val
 35 40 45

Leu Cys Ala Ser Phe Met Ser Phe Gly Val Lys Arg Arg Trp Phe Ala
 50 55 60
 Leu Gly Ala Ala Leu Gln Leu Ala Ile Ser Thr Tyr Ala Ala Tyr Ile
 65 70 75 80
 Gly Gly Tyr Val His Tyr Gly Asp Trp Leu Lys Val Arg Met Tyr Ser
 85 90 95
 Arg Thr Val Ala Ile Ile Gly Gly Phe Leu Val Leu Ala Ser Gly Ala
 100 105 110
 Gly Glu Leu Tyr Arg Arg Lys Pro Arg Ser Arg Ser Leu Gln Ser Thr
 115 120 125
 Gly Gln Val Phe Leu Gly Ile Tyr Leu Ile Cys Val Ala Tyr Ser Leu
 130 135 140
 Gln His Ser Lys Glu Asp Arg Leu Ala Tyr Leu Asn His Leu Pro Gly
 145 150 155 160
 Gly Glu Leu Met Ile Gln Leu Phe Phe Val Leu Tyr Gly Ile Leu Ala
 165 170 175
 Leu Ala Phe Leu Ser Gly Tyr Tyr Val Thr Leu Ala Ala Gln Ile Leu
 180 185 190
 Ala Val Leu Leu Pro Pro Val Met Leu Leu Ile Asp Gly Asn Val Ala
 195 200 205
 Tyr Trp His Asn Thr Arg Arg Val Glu Phe Trp Asn Gln Met Lys Leu
 210 215 220
 Leu Gly Glu Ser Val Gly Ile Phe Gly Thr Ala Val Ile Leu Ala Thr
 225 230 235 240

Asp Gly

<210> 132
 <211> 313
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (313)
 <223> Xaa equals stop translation

<400> 132
 Met Glu Ser Leu Tyr Asp Leu Trp Glu Phe Tyr Leu Pro Tyr Leu Tyr
 1 5 10 15
 Ser Cys Ile Ser Leu Met Gly Cys Leu Leu Leu Leu Cys Thr Pro
 20 25 30
 Val Gly Leu Ser Arg Met Phe Thr Val Met Gly His Leu Leu Val Lys
 35 40 45

Pro Thr Ile Leu Glu Asp Leu Asp Glu Gln Ile Tyr Ile Ile Thr Leu
 50 55 60
 Glu Glu Glu Ala Leu Gln Arg Arg Leu Asn Gly Leu Ser Ser Ser Val
 65 70 75 80
 Glu Tyr Asn Ile Met Glu Leu Glu Gln Glu Leu Glu Asn Val Lys Thr
 85 90 95
 Leu Lys Thr Lys Leu Glu Arg Arg Lys Lys Ala Ser Ala Trp Glu Arg
 100 105 110
 Asn Leu Val Tyr Pro Ala Val Met Val Leu Leu Leu Ile Glu Thr Ser
 115 120 125
 Ile Ser Val Leu Leu Val Ala Cys Asn Ile Leu Cys Leu Leu Val Asp
 130 135 140
 Glu Thr Ala Met Pro Lys Gly Thr Arg Gly Pro Gly Ile Gly Asn Ala
 145 150 155 160
 Ser Leu Ser Thr Phe Gly Phe Val Gly Ala Ala Leu Glu Ile Ile Leu
 165 170 175
 Ile Phe Tyr Leu Met Val Ser Ser Val Val Gly Phe Tyr Ser Leu Arg
 180 185 190
 Phe Phe Gly Asn Phe Thr Pro Lys Lys Asp Asp Thr Thr Met Thr Lys
 195 200 205
 Ile Ile Gly Asn Cys Val Ser Ile Leu Val Leu Ser Ser Ala Leu Pro
 210 215 220
 Val Met Ser Arg Thr Leu Gly Ile Thr Arg Phe Asp Leu Leu Gly Asp
 225 230 235 240
 Phe Gly Arg Phe Asn Trp Leu Gly Asn Phe Tyr Ile Val Leu Ser Tyr
 245 250 255
 Asn Leu Leu Phe Ala Ile Val Thr Thr Leu Cys Leu Val Arg Lys Phe
 260 265 270
 Thr Ser Ala Val Arg Glu Glu Leu Phe Lys Ala Leu Gly Leu His Lys
 275 280 285
 Leu His Leu Pro Asn Thr Ser Arg Asp Ser Glu Thr Ala Lys Pro Ser
 290 295 300
 Val Asn Gly His Gln Lys Ala Leu Xaa
 305 310

<210> 133

<211> 183

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (183)

<223> Xaa equals stop translation

<400> 133

Met Met Val Cys Ser Ile Met Met Tyr Phe Leu Leu Gly Ile Thr Leu
 1 5 10 15

Leu Arg Ser Tyr Met Gln Ser Val Trp Thr Glu Glu Ser Gln Cys Thr
 20 25 30

Leu Leu Asn Ala Ser Ile Thr Glu Thr Phe Asn Cys Ser Phe Ser Cys
 35 40 45

Gly Pro Asp Cys Trp Lys Leu Ser Gln Tyr Pro Cys Leu Gln Val Tyr
 50 55 60

Val Asn Leu Thr Ser Ser Gly Glu Lys Leu Leu Leu Tyr His Thr Glu
 65 70 75 80

Glu Thr Ile Lys Ile Asn Gln Lys Cys Ser Tyr Ile Pro Lys Cys Gly
 85 90 95

Lys Asn Phe Glu Glu Ser Met Ser Leu Val Asn Val Val Met Glu Asn
 100 105 110

Phe Arg Lys Tyr Gln His Phe Ser Cys Tyr Ser Asp Pro Glu Gly Asn
 115 120 125

Gln Lys Ser Val Ile Leu Thr Lys Leu Tyr Ser Ser Asn Val Leu Phe
 130 135 140

His Ser Leu Phe Trp Pro Thr Cys Met Met Ala Gly Gly Val Ala Ile
 145 150 155 160

Val Ala Met Val Lys Leu Thr Gln Tyr Leu Ser Leu Leu Cys Glu Arg
 165 170 175

Ile Gln Arg Ile Asn Arg Xaa
 180

<210> 134

<211> 147

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (147)

<223> Xaa equals stop translation

<400> 134

Met Trp Lys Leu Trp Arg Ala Glu Glu Gly Ala Ala Ala Leu Gly Gly
 1 5 10 15

Ala Leu Phe Leu Leu Phe Ala Leu Gly Val Arg Gln Leu Leu Lys
 20 25 30

Gln Arg Arg Pro Met Gly Phe Pro Pro Gly Pro Pro Gly Leu Pro Phe
 35 40 45
 Ile Gly Asn Ile Tyr Ser Leu Ala Ala Ser Ser Glu Leu Pro His Val
 50 55 60
 Tyr Met Arg Lys Gln Ser Gln Val Tyr Gly Glu Val Gln Pro Arg Arg
 65 70 75 80
 Ala Pro Gly Arg Glu Gly Arg Gln Ala Gly Pro Gly Trp Pro Gly Pro
 85 90 95
 Ser Trp Leu Asp Leu Trp Pro Pro Leu Gly Arg Leu Val Gly Thr Ser
 100 105 110
 Pro Cys Ala Gly Cys Pro Leu Arg Asp Thr Arg Phe Pro Gly Leu Glu
 115 120 125
 Gly Arg Ser Pro Arg Arg Arg Ala Pro Leu Gln Gly Glu Pro Arg Pro
 130 135 140
 Cys Arg Xaa
 145

<210> 135
 <211> 122
 <212> PRT
 <213> Homo sapiens

<400> 135
 Met Arg Val Arg Ile Gly Leu Thr Leu Leu Leu Cys Ala Val Leu Leu
 1 5 10 15
 Ser Leu Ala Ser Ala Ser Ser Asp Glu Glu Gly Ser Gln Asp Glu Ser
 20 25 30
 Leu Asp Ser Lys Thr Thr Leu Thr Ser Asp Glu Ser Val Lys Asp His
 35 40 45
 Thr Thr Ala Gly Arg Val Val Ala Gly Gln Ile Phe Leu Asp Ser Glu
 50 55 60
 Glu Ser Glu Leu Glu Ser Ser Ile Gln Glu Glu Asp Ser Leu Lys
 65 70 75 80
 Ser Gln Glu Gly Glu Ser Val Thr Glu Asp Ile Ser Phe Leu Glu Ser
 85 90 95
 Pro Asn Pro Glu Asn Lys Asp Tyr Glu Glu Pro Lys Lys Val Arg Lys
 100 105 110
 Pro Gly Ser Leu Asp Ile Phe Leu Ala Phe
 115 120

<210> 136
 <211> 112
 <212> PRT

<213> Homo sapiens

<400> 136

Met Ala Arg Gly Ser Leu Arg Arg Leu Leu Arg Leu Leu Val Leu Gly
 1 5 10 15

Leu Trp Leu Ala Leu Leu Arg Ser Val Ala Gly Glu Gln Ala Pro Gly
 20 25 30

Thr Ala Pro Cys Ser Arg Gly Ser Ser Trp Ser Ala Asp Leu Asp Lys
 35 40 45

Cys Met Asp Cys Ser Thr Ser Cys Pro Leu Pro Ala Ala Leu Ala His
 50 55 60

Pro Trp Gly Arg Ser Glu Pro Asp Leu Arg Ala Gly Ala Ala Phe Trp
 65 70 75 80

Leu Phe Gly Leu Glu Thr Met Pro Gln Arg Glu Lys Phe Thr Thr Pro
 85 90 95

Ile Glu Glu Thr Gly Gly Glu Gly Cys Pro Ala Val Ala Leu Ile Gln
 100 105 110

<210> 137

<211> 140

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (140)

<223> Xaa equals stop translation

<400> 137

Met Leu Leu Gly Pro Val Pro Ile Leu His Ile Lys Ser Gln Leu Trp
 1 5 10 15

Leu Leu Val Leu Ile Leu Val Val Ser Gly Leu Ser Ala Gly Met Ser
 20 25 30

Ile Ile Pro Thr Phe Pro Glu Ile Leu Ser Cys Ala His Glu Asn Gly
 35 40 45

Phe Glu Glu Gly Leu Ser Thr Leu Gly Leu Val Ser Gly Leu Phe Ser
 50 55 60

Ala Met Trp Ser Ile Gly Ala Phe Met Gly Pro Thr Leu Gly Gly Phe
 65 70 75 80

Leu Tyr Glu Lys Ile Gly Phe Glu Trp Ala Ala Ala Ile Gln Gly Leu
 85 90 95

Trp Ala Leu Ile Ser Gly Leu Ala Met Gly Leu Phe Tyr Leu Leu Glu
 100 105 110

Tyr Ser Arg Arg Lys Arg Ser Lys Ser Gln Asn Ile Leu Ser Thr Glu
 115 120 125

Glu Glu Arg Thr Thr Leu Leu Pro Asn Glu Thr Xaa
 130 135 140

<210> 138

<211> 404

<212> PRT

<213> Homo sapiens

<400> 138

Met Arg Leu Gln Asp Val Tyr Met Leu Asn Val Lys Gly Leu Ala Arg
 1 5 10 15

Gly Val Phe Gln Arg Val Thr Gly Ser Ala Ile Thr Asp Leu Tyr Ser
 20 25 30

Pro Lys Arg Leu Phe Ser Leu Thr Gly Asp Asp Cys Phe Gln Val Gly
 35 40 45

Lys Val Ala Tyr Asp Met Gly Asp Tyr Tyr His Ala Ile Pro Trp Leu
 50 55 60

Glu Glu Ala Val Ser Leu Phe Arg Gly Ser Tyr Gly Glu Trp Lys Thr
 65 70 75 80

Glu Asp Glu Ala Ser Leu Glu Asp Ala Leu Asp His Leu Ala Phe Ala
 85 90 95

Tyr Phe Arg Ala Gly Asn Val Ser Cys Ala Leu Ser Leu Ser Arg Glu
 100 105 110

Phe Leu Leu Tyr Ser Pro Asp Asn Lys Arg Met Ala Arg Asn Val Leu
 115 120 125

Lys Tyr Glu Arg Leu Leu Ala Glu Ser Pro Asn His Val Val Ala Glu
 130 135 140

Ala Val Ile Gln Arg Pro Asn Ile Pro His Leu Gln Thr Arg Asp Thr
 145 150 155 160

Tyr Glu Gly Leu Cys Gln Thr Leu Gly Ser Gln Pro Thr Leu Tyr Gln
 165 170 175

Ile Pro Ser Leu Tyr Cys Ser Tyr Glu Thr Asn Ser Asn Ala Tyr Leu
 180 185 190

Leu Leu Gln Pro Ile Arg Lys Glu Val Ile His Leu Glu Pro Tyr Ile
 195 200 205

Ala Leu Tyr His Asp Phe Val Ser Asp Ser Glu Ala Gln Lys Ile Arg
 210 215 220

Glu Leu Ala Glu Pro Trp Leu Gln Arg Ser Val Val Ala Ser Gly Glu
 225 230 235 240

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<210> 139
<211> 96
<212> PRT
<213> Homo sapiens
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<220>
<221> SITE
<222> (96)
<223> Xaa equals stop translation
```

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<400> 139
Met Lys Ala Pro His Thr Gly Val Leu His Leu Gly Ser Val Trp Val
  1              5              10              15
Phe Leu Gly Pro Phe Leu Leu Gly Val Gly Tyr Thr Leu Thr Phe Asn
      20              25              30
Pro Leu Ser Gly Cys Met Ser Thr Val Arg Trp Leu Asn Ser Asn Ile
      35              40              45
Thr Ala Asn Arg Thr Leu Ser Arg Ser Val Cys His Val Thr Pro Leu
      50              55              60
His Arg Ser Leu Ser Pro His Asp Gly Glu Tyr Leu Arg Gln Met Leu
      65              70              75              80

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100

Leu Asn Ser Ser Ser Arg Ala Gly Glu Ala Gly Ser Trp Gly Tyr Xaa
 85 90 95

<210> 140
 <211> 240
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (240)
 <223> Xaa equals stop translation

<400> 140
 Met Gly Ser Cys Ala Arg Leu Leu Leu Leu Trp Gly Cys Thr Val Val
 1 5 10 15
 Ala Ala Gly Leu Ser Gly Val Ala Gly Val Ser Ser Arg Cys Glu Lys
 20 25 30
 Ala Cys Asn Pro Arg Met Gly Asn Leu Ala Leu Gly Arg Lys Leu Trp
 35 40 45
 Ala Asp Thr Thr Cys Gly Gln Asn Ala Thr Glu Leu Tyr Cys Phe Tyr
 50 55 60
 Ser Glu Asn Thr Asp Leu Thr Cys Arg Gln Pro Lys Cys Asp Lys Cys
 65 70 75 80
 Asn Ala Ala Tyr Pro His Leu Ala His Leu Pro Ser Ala Met Ala Asp
 85 90 95
 Ser Ser Phe Arg Phe Pro Arg Thr Trp Trp Gln Ser Ala Glu Asp Val
 100 105 110
 His Arg Glu Lys Ile Gln Leu Asp Leu Glu Ala Glu Phe Tyr Phe Thr
 115 120 125
 His Leu Ile Val Met Phe Lys Ser Pro Arg Pro Ala Ala Met Val Leu
 130 135 140
 Asp Arg Ser Gln Asp Phe Gly Lys Thr Trp Lys Pro Tyr Lys Tyr Phe
 145 150 155 160
 Ala Thr Asn Cys Ser Ala Thr Phe Gly Leu Glu Asp Asp Val Val Lys
 165 170 175
 Lys Gly Ala Ile Cys Thr Ser Lys Tyr Ser Ser Pro Phe Pro Cys Thr
 180 185 190
 Gly Arg Lys Val Ile Phe Lys Ala Leu Ser Pro Pro Tyr Asp Thr Glu
 195 200 205
 Asn Pro Tyr Ser Ala Lys Val Gln Glu Gln Leu Lys Ile Thr Asn Leu

210	215	220
Pro Arg Ala Ala Ala Glu Thr Thr Val Leu Ser Leu Ser Glu Lys Xaa		
225	230	235 240

<210> 141
 <211> 54
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (54)
 <223> Xaa equals stop translation

<400> 141
 Met Met Ile Ser Gly Leu Lys Leu Leu Val Leu Phe Leu Lys Phe Ala
 1 5 10 15
 Pro Glu Asn Tyr Cys Leu Ser Thr Glu Thr Leu Gln Met Pro Asn Arg
 20 25 30
 His Leu Arg Leu Ser Lys Ala Thr Cys Tyr Leu Met Lys Cys Leu Leu
 35 40 45

Pro Ser Tyr Phe Glu Xaa
 50

<210> 142
 <211> 67
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (67)
 <223> Xaa equals stop translation

<400> 142
 Met Arg Ser Leu Ile Ser Ser His Pro Cys Gln His Leu Leu Leu Leu
 1 5 10 15
 Leu Leu Leu Leu Phe Leu Ile Leu Ala Ile Leu Val Asp Val Lys Trp
 20 25 30
 Tyr Leu Val Leu Phe Ile Cys Ile Ser Leu Met Thr Ser Asp Val Glu
 35 40 45
 His Leu Phe Met Cys Leu Leu Ala Ile Arg Ile Ser Ser Trp Arg Asn
 50 55 60
 Val Tyr Xaa
 65

<210> 143
 <211> 108
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (48)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (55)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (58)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (67)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 143
 Met Phe Tyr Lys Leu Thr Leu Ile Leu Cys Glu Leu Ser Val Ala Gly
 1 5 10 15
 Val Thr Gln Ala Ala Ser Gln Arg Pro Leu Gln Arg Leu Pro Arg His
 20 25 30
 Ile Cys Ser Gln Arg Asn Pro Pro Gly Arg Cys Leu Leu Lys Ala Xaa
 35 40 45
 Leu Gln Thr Thr Trp Gly Xaa Pro Asp Xaa Gln Phe Pro Gly Cys Pro
 50 55 60
 His Pro Xaa Arg Val Thr Leu Asn Ala Arg Gln Met Gly Asn Gly Lys
 65 70 75 80
 Glu Lys Lys Ala Ala Asp Leu Lys Leu Lys Phe Pro Gln Lys Arg Phe
 85 90 95
 Tyr Leu Ser Ala Phe Ser Glu Arg Ile Lys Ala Phe
 100 105

<210> 144
 <211> 84
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (84)
 <223> Xaa equals stop translation

<400> 144

Met Ala Ser Val Gly Thr Thr Leu Val Ser Pro Leu Leu Cys Leu Leu
 1 5 10 15

Ile Pro Thr Arg Val Ser Asp Pro Trp Leu Gln Asn Thr Pro Leu His
 20 25 30

Pro Trp Lys Thr Ile Thr Ile Ile Asp Tyr Tyr Leu Ser Leu Gly Phe
 35 40 45

Leu Gly Trp Thr Gly Leu Ser Trp Val Val His Phe Gly Ala Ser Ala
 50 55 60

Val Met Gly Arg Gln Trp Leu Gly Ser Leu Gln Arg Leu Pro Cys Ile
 65 70 75 80

Ser Gly Ser Xaa

<210> 145

<211> 166

<212> PRT

<213> Homo sapiens

<400> 145

Met Gly Ser Arg Phe Leu Leu Val Leu Leu Ser Gly Leu Thr Val Leu
 1 5 10 15

Leu Ala Leu Pro Gly Ser Glu Ala Lys Asn Ser Gly Ala Ser Cys Pro
 20 25 30

Pro Cys Pro Lys Tyr Ala Ser Cys His Asn Ser Thr His Cys Thr Cys
 35 40 45

Glu Asp Gly Phe Arg Ala Arg Ser Gly Arg Thr Tyr Phe His Asp Ser
 50 55 60

Ser Glu Lys Cys Glu Asp Ile Asn Glu Cys Glu Thr Gly Leu Ala Lys
 65 70 75 80

Cys Lys Tyr Lys Ala Tyr Cys Arg Asn Lys Val Gly Gly Tyr Ile Cys
 85 90 95

Ser Cys Leu Val Lys Tyr Thr Leu Phe Asn Phe Leu Ala Gly Ile Ile
 100 105 110

Asp Tyr Asp His Pro Asp Cys Tyr Glu Asn Asn Ser Gln Gly Thr Thr
 115 120 125

Gln Ser Asn Val Asp Ile Trp Val Ser Gly Val Lys Pro Gly Phe Gly
 130 135 140

Lys Gln Leu Val Arg Ile Thr Met Pro Phe Ser Tyr Pro Asn Ile Asn
 145 150 155 160

Met Ser Ser Cys Asp Phe
 165

<210> 146
 <211> 70
 <212> PRT
 <213> Homo sapiens

<400> 146
 Met Lys Pro Lys His Leu Glu Trp Cys Leu Ala His Ser Trp Cys Val
 1 5 10 15
 Ile Trp Leu Ser Phe Val Ser Pro Pro Thr Ser His Leu Glu Cys Asp
 20 25 30
 Gly Phe Pro Gly Ser Leu Leu Pro Pro Cys Glu Glu Gly Arg Cys Phe
 35 40 45
 Pro Phe Thr Phe His His His Asp Cys His Gly Cys Ser Pro Leu Gln
 50 55 60
 Ser Ser Pro Gly Gln His
 65 70

<210> 147
 <211> 412
 <212> PRT
 <213> Homo sapiens

<400> 147
 Met Cys Cys Trp Pro Leu Leu Leu Leu Trp Gly Leu Leu Pro Gly Thr
 1 5 10 15
 Ala Ala Gly Gly Ser Gly Arg Thr Tyr Pro His Arg Thr Leu Leu Asp
 20 25 30
 Ser Glu Gly Lys Tyr Trp Leu Gly Trp Ser Gln Arg Gly Ser Gln Ile
 35 40 45
 Ala Phe Arg Leu Gln Val Arg Thr Ala Gly Tyr Val Gly Phe Gly Phe
 50 55 60
 Ser Pro Thr Gly Ala Met Ala Ser Ala Asp Ile Val Val Gly Gly Val
 65 70 75 80
 Ala His Gly Arg Pro Tyr Leu Gln Asp Tyr Phe Thr Asn Ala Asn Arg
 85 90 95
 Glu Leu Lys Lys Asp Ala Gln Gln Asp Tyr His Leu Glu Tyr Ala Met
 100 105 110
 Glu Asn Ser Thr His Thr Ile Ile Glu Phe Thr Arg Glu Leu His Thr
 115 120 125
 Cys Asp Ile Asn Asp Lys Ser Ile Thr Asp Ser Thr Val Arg Val Ile
 130 135 140
 Trp Ala Tyr His His Glu Asp Ala Gly Glu Ala Gly Pro Lys Tyr His
 145 150 155 160

Asp	Ser	Asn	Arg	Gly	Thr	Lys	Ser	Leu	Arg	Leu	Leu	Asn	Pro	Glu	Lys	
				165					170							
								175								
Thr	Ser	Val	Leu	Ser	Thr	Ala	Leu	Pro	Tyr	Phe	Asp	Leu	Val	Asn	Gln	
				180					185							
								190								
Asp	Val	Pro	Ile	Pro	Asn	Lys	Asp	Thr	Thr	Tyr	Trp	Cys	Gln	Met	Phe	
				195					200							
								205								
Lys	Ile	Pro	Val	Phe	Gln	Glu	Lys	His	His	Val	Ile	Lys	Val	Glu	Pro	
				210					215							
								220								
Val	Ile	Gln	Arg	Gly	His	Glu	Ser	Leu	Val	His	His	Ile	Leu	Leu	Tyr	
				225					230							
								235								
Gln	Cys	Ser	Asn	Asn	Phe	Asn	Asp	Ser	Val	Leu	Glu	Ser	Gly	His	Glu	
				245					250							
								255								
Cys	Tyr	His	Pro	Asn	Met	Pro	Asp	Ala	Phe	Leu	Thr	Cys	Glu	Thr	Val	
				260					265							
								270								
Ile	Phe	Ala	Trp	Ala	Ile	Gly	Gly	Glu	Gly	Phe	Ser	Tyr	Pro	Pro	His	
				275					280							
								285								
Val	Gly	Leu	Ser	Leu	Gly	Thr	Pro	Leu	Asp	Pro	His	Tyr	Val	Leu	Leu	
				290					295							
								300								
Glu	Val	His	Tyr	Asp	Asn	Pro	Thr	Tyr	Glu	Glu	Gly	Leu	Ile	Asp	Asn	
				305					310							
								315								
Ser	Gly	Leu	Arg	Leu	Phe	Tyr	Thr	Met	Asp	Ile	Arg	Lys	Tyr	Asp	Ala	
				325					330							
								335								
Gly	Val	Ile	Glu	Ala	Gly	Leu	Trp	Val	Ser	Leu	Phe	His	Thr	Ile	Pro	
				340					345							
								350								
Pro	Gly	Met	Pro	Glu	Phe	Gln	Ser	Glu	Gly	His	Cys	Thr	Leu	Glu	Cys	
				355					360							
								365								
Leu	Glu	Glu	Leu	Trp	Lys	Pro	Lys	Ser	Gln	Val	Glu	Phe	Met	Cys	Leu	
				370					375							
								380								
Leu	Phe	Phe	Ser	Met	Leu	Thr	Trp	Leu	Ala	Glu	His	Gln	Ala	Ala	Ser	
				385					390							
								395								
Phe	Ser	Lys	Arg	Glu	Gly	Asn	Glu	Ile	Thr	Cys	Leu					
				405					410							

<210> 148

<211> 85

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (85)

<223> Xaa equals stop translation

106

<400> 148

Met Asn Val Phe Leu Pro Pro Ala Leu Gly Thr Trp Gly Val Ala Arg
 1 5 10 15
 Phe Phe Pro His Leu Val Pro Glu Arg Trp Cys Leu Val Phe Cys Cys
 20 25 30
 Trp Ile Phe Phe Phe Phe Phe Phe Cys Thr Lys Val Ala Thr Arg
 35 40 45
 Ser Val Leu Gly Asp Gln Ala Gly Leu Gly Val Gly Gly Pro His Leu
 50 55 60
 Pro Leu Pro Gly Ser His Ser Val Ser Val Pro Glu Lys Thr Ile Phe
 65 70 75 80
 Ser Leu Lys Gln Xaa
 85

<210> 149

<211> 154

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (154)

<223> Xaa equals stop translation

<400> 149

Met Gly Arg Leu Pro Leu Leu Arg Arg Val Leu Lys Gly Leu Gln Leu
 1 5 10 15
 Leu Leu Ser Leu Leu Ala Phe Ile Cys Glu Glu Val Val Ser Gln Cys
 20 25 30
 Thr Leu Cys Gly Gly Leu Tyr Phe Phe Glu Phe Val Ser Cys Ser Ala
 35 40 45
 Phe Leu Leu Ser Leu Leu Ile Leu Ile Val Tyr Cys Thr Pro Phe Tyr
 50 55 60
 Glu Arg Val Asp Thr Thr Lys Val Lys Ser Ser Asp Phe Tyr Ile Thr
 65 70 75 80
 Leu Gly Thr Gly Cys Val Phe Leu Leu Ala Ser Ile Ile Phe Val Ser
 85 90 95
 Thr His Asp Arg Thr Ser Ala Glu Ile Ala Ala Ile Val Phe Gly Phe
 100 105 110
 Ile Ala Ser Phe Met Phe Leu Leu Asp Phe Ile Thr Met Leu Tyr Glu
 115 120 125
 Lys Arg Gln Glu Ser Gln Leu Arg Lys Pro Glu Asn Thr Thr Arg Ala
 130 135 140
 Glu Ala Leu Thr Glu Pro Leu Asn Ala Xaa

145

150

<210> 150

<211> 130

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (130)

<223> Xaa equals stop translation

<400> 150

Met Arg Gly His Leu Ala Gly Phe Pro Ala Leu Ser Gly Leu Ala Ser
 1 5 10 15

Val Cys Leu Trp Ala Thr Phe Ser Ala Gln Leu Pro Gly Pro Val Ala
 20 25 30

Ala Thr Ser Trp Thr Pro Ala Pro Leu Gly Cys Ser Ala Ala Arg Ser
 35 40 45

Gly Pro Glu Lys Arg Leu Gly Thr Ala Ala Pro Gly Ser Ala Ala Ser
 50 55 60

Leu Ala Gln Ala Gly Pro Gly Ala Pro Cys Arg Val Leu Pro Val Asp
 65 70 75 80

Pro Ala Pro Ala Ala Leu Asn Val Arg Glu Pro Gly Trp Leu Gly Gly
 85 90 95

Leu Phe Asp Gly Ala Leu Leu Gln Val Leu Leu Asn Phe Leu Arg Lys
 100 105 110

Ser Thr Asp Val Leu Met Asp Thr Arg Glu Ala Glu Ser Leu Glu Val
 115 120 125

Glu Xaa
 130

<210> 151

<211> 62

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (62)

<223> Xaa equals stop translation

<400> 151

Met Leu Phe Trp Ala Tyr Pro Ile Cys Val Phe Ile Asp Ser Leu Ser
 1 5 10 15

Cys Gln Pro Cys Leu Trp Ser Thr Gly Ala Thr Ser His Phe Asn Ser
 20 25 30

108

Pro Thr Thr Ser Pro Leu Phe Thr Leu Phe Met Pro Cys Ala Leu Ala
 35 40 45

Pro Asn Pro Phe Thr Gln Leu Gly Lys Leu Asp Asp Arg Xaa
 50 55 60

<210> 152

<211> 225

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (225)

<223> Xaa equals stop translation

<400> 152

Met Gly Ile Phe Pro Gly Ile Ile Leu Ile Phe Leu Arg Val Lys Phe
 1 5 10 15

Ala Thr Ala Ala Val Ile Val Ser Gly His Gln Lys Ser Thr Thr Val
 20 25 30

Ser His Glu Met Ser Gly Leu Asn Trp Lys Pro Phe Val Tyr Gly Gly
 35 40 45

Leu Ala Ser Ile Val Ala Glu Phe Gly Thr Phe Pro Val Asp Leu Thr
 50 55 60

Lys Thr Arg Leu Gln Val Gln Gly Gln Ser Ile Asp Ala Arg Phe Lys
 65 70 75 80

Glu Ile Lys Tyr Arg Gly Met Phe His Ala Leu Phe Arg Ile Cys Lys
 85 90 95

Glu Glu Gly Val Leu Ala Leu Tyr Ser Gly Ile Ala Pro Ala Leu Leu
 100 105 110

Arg Gln Ala Ser Tyr Gly Thr Ile Lys Ile Gly Ile Tyr Gln Ser Leu
 115 120 125

Lys Arg Leu Phe Val Glu Arg Leu Glu Asp Glu Thr Leu Leu Ile Asn
 130 135 140

Met Ile Cys Gly Val Val Ser Gly Val Ile Ser Ser Thr Ile Ala Asn
 145 150 155 160

Pro Thr Asp Val Leu Lys Ile Arg Met Gln Ala Gln Gly Ser Leu Phe
 165 170 175

Gln Gly Ser Met Ile Gly Ser Phe Ile Asp Ile Tyr Gln Gln Glu Gly
 180 185 190

Thr Arg Gly Leu Trp Arg Val Ser Thr Leu Phe Leu Leu Ser Tyr
 195 200 205

Thr Leu Ser Ser Tyr Asn Leu Gln Arg Ile Phe Phe Tyr Ile Lys Thr
 210 215 220

Xaa
225

<210> 153
<211> 69
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (69)
<223> Xaa equals stop translation

<400> 153
Met Leu Met Leu Leu Thr Leu Leu Val Leu Gly Met Val Trp Val Ala
1 5 10 15
Ser Ala Ile Val Asp Lys Asn Lys Ala Asn Arg Glu Ser Leu Tyr Asp
20 25 30
Phe Trp Glu Tyr Tyr Leu Pro Tyr Leu Tyr Ser Cys Ile Ser Phe Leu
35 40 45
Gly Val Leu Leu Leu Leu Ala Ala Gly Arg Pro Gly Gly Ala Ala Val
50 55 60
Leu Leu Ser Leu Xaa
65

<210> 154
<211> 84
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (84)
<223> Xaa equals stop translation

<400> 154
Met Tyr Gly Val Cys Leu Cys Val Ile Val Cys Val Ser Gly Val Ser
1 5 10 15
Leu Cys Leu Tyr Val Trp Gly Val Ser Val Cys Asp Cys Val Ser Val
20 25 30
Phe Met Cys Val Cys Leu Cys Val Ile Phe Cys Val Tyr Gly Lys Pro
35 40 45
Arg Thr Glu His Tyr His Ser Pro His Leu Ala Lys Gln Lys Ala Phe
50 55 60
Arg Glu Met Cys Gly Arg His Asp Val Ser Ala Ala Gly Ile Phe Gln
65 70 75 80
Ser Tyr Val Xaa

<210> 155
<211> 61
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (61)
<223> Xaa equals stop translation

<400> 155
Met His Val Leu Leu Phe Ser Phe Leu Ile Pro Phe Leu Leu Leu Ser
1 5 10 15
Pro Val Gly Val Thr Cys Asn Ser His Met Leu Glu Arg Gln Val Ser
20 25 30
Trp Leu Lys Lys Arg Ser Thr Gln Ala Ser Gln Gln Phe Asn Lys Phe
35 40 45
Leu Arg Gly Ile Ser Asn Val Gly Arg Ile Val Ile Xaa
50 55 60

<210> 156
<211> 84
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (84)
<223> Xaa equals stop translation

<400> 156
Met Cys Leu Leu Val Glu Tyr Ser Leu Met Ile Leu Thr Ile Ile Pro
1 5 10 15
Ser Leu Leu Ser Phe Val Leu Cys Leu Lys Gly Ile Lys His Gly Asn
20 25 30
Tyr Ile Phe Gln Thr Pro Leu Pro Glu Gly Tyr Gly Trp Ile Ser Ala
35 40 45
Met Ser Gly Leu Cys Ile Lys Phe Gly Arg Arg Lys Arg Arg Lys Thr
50 55 60
Trp Leu Leu Gln Val Gly Thr Leu Ala Thr Ile Asp Thr Glu Phe Ala
65 70 75 80
Arg Ser Cys Xaa

<210> 157
<211> 162

111

<212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (162)
 <223> Xaa equals stop translation

<400> 157
 Met Ala Leu Ser Leu Thr Leu Cys Phe Val Met Phe Trp Thr Pro Asn
 1 5 10 15
 Val Ser Glu Lys Ile Leu Ile Asp Ile Ile Gly Val Asp Phe Ala Phe
 20 25 30
 Ala Glu Leu Cys Val Val Pro Leu Arg Ile Phe Ser Phe Phe Pro Val
 35 40 45
 Pro Val Thr Val Arg Ala His Leu Thr Gly Trp Leu Met Thr Leu Lys
 50 55 60
 Lys Thr Phe Val Leu Ala Pro Ser Ser Val Leu Arg Ile Ile Val Leu
 65 70 75 80
 Ile Ala Ser Leu Val Val Leu Pro Tyr Leu Gly Val His Gly Ala Thr
 85 90 95
 Leu Gly Val Gly Ser Leu Leu Ala Gly Phe Val Gly Glu Ser Thr Met
 100 105 110
 Val Ala Ile Ala Ala Cys Tyr Val Tyr Arg Lys Gln Lys Lys Lys Met
 115 120 125
 Glu Asn Glu Ser Ala Thr Glu Gly Glu Asp Ser Ala Met Thr Asp Met
 130 135 140
 Pro Pro Thr Glu Glu Val Thr Asp Ile Val Glu Met Arg Glu Glu Asn
 145 150 155 160
 Glu Xaa

<210> 158
 <211> 146
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (96)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (107)
 <223> Xaa equals any of the naturally occurring L-amino acids
 <220>

<221> SITE
 <222> (111)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (115)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (122)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (132)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 158
 Met Glu Pro Gln Leu Gly Pro Glu Ala Ala Leu Arg Pro Gly Trp
 1 5 10 15
 Leu Ala Leu Leu Leu Trp Val Ser Ala Leu Ser Cys Ser Phe Ser Leu
 20 25 30
 Pro Ala Ser Ser Leu Ser Ser Leu Val Pro Gln Val Arg Thr Ser Tyr
 35 40 45
 Asn Phe Gly Arg Thr Phe Leu Gly Leu Asp Lys Cys Asn Ala Cys Ile
 50 55 60
 Gly Thr Ser Ile Cys Lys Lys Phe Phe Lys Glu Glu Ile Arg Ser Asp
 65 70 75 80
 Asn Trp Leu Ala Ser His Leu Gly Thr Ala Ser Arg Phe Pro Leu Xaa
 85 90 95
 Ser Tyr Pro Cys Lys Leu Leu Gln Met Ile Xaa Lys Ile Trp Xaa Pro
 100 105 110
 Cys Gly Xaa Leu Leu Thr Gly Gln Gln Xaa Ser Asn Glu Ile Ser Lys
 115 120 125
 Gln Glu Ile Xaa Cys Leu Leu His Pro Pro Pro Lys Asn Leu His Ile
 130 135 140
 Asp Val
 145

<210> 159
 <211> 143
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (143)

<223> Xaa equals stop translation

<400> 159

```

Met Trp Trp Ala Val Met Gly Gly Val Ile Gly Ser Trp Leu Ser Pro
 1           5           10           15

Leu Ser Ile Ala Glu Cys Cys His Asp Leu Trp Thr Ser Gln Ser Cys
      20           25           30

Glu His Ala Gly Ala Leu Cys Gly Asp Leu Leu Cys Ala Cys Arg Lys
      35           40           45

Val Gly Val Trp Cys Ala Leu Gln Gln His Trp Trp Asn Arg Cys Val
      50           55           60

Cys Pro His Ala Val Ile Arg Val His Cys Thr Gly Ala Ser Tyr Thr
      65           70           75           80

Leu Gln Lys Ile Cys Ser Cys Asn Pro Lys Phe Met Gly Arg His Pro
      85           90           95

His Arg Trp Gln Gln Ile Arg Lys Cys Ser Gln Pro Val Leu Arg Gly
      100          105          110

Ser Arg Ala Ala Phe Ile Trp Val Arg Leu Ala Ala Leu Asn Phe Ile
      115          120          125

Ser Ser Phe Arg Cys Ile Ser Leu Ile Ser Tyr Ser Ala Phe Xaa
      130          135          140

```

<210> 160

<211> 51

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (51)

<223> Xaa equals stop translation

<400> 160

```

Met Lys Val Ser Asp Phe Asn Phe Leu Ile Phe Leu Ile Phe Ala Leu
 1           5           10           15

Phe Leu Thr Leu Glu Ala Phe Leu Lys Phe Thr Lys Arg Val Leu Ala
      20           25           30

Val Val Gly Asn Leu Pro Glu Pro Pro Ile Ile Lys Thr Ile Gly Phe
      35           40           45

Leu Tyr Xaa
      50

```

<210> 161

<211> 65

<212> PRT

<213> Homo sapiens

<220>
<221> SITE
<222> (65)
<223> Xaa equals stop translation

<400> 161
Met Val Trp Ser Ala Ala Pro Ala Pro Cys Cys Leu Leu Gly Val Leu
1 5 10 15
Gly Leu Val Gln Val Leu Gly Ala Gln Ala Val Gly Pro Trp Thr Ala
20 25 30
Ser Ala Cys Leu Gly Ala Ala Gln Ala Gln Pro Cys Arg Pro Cys Lys
35 40 45
Glu Ser Ser Leu Arg Leu Phe Ser Ala Ser Ala Pro Ser Met Thr His
50 55 60
Xaa
65

<210> 162
<211> 59
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (59)
<223> Xaa equals stop translation

<400> 162
Met Glu Lys Tyr Cys Leu Gly Asn Asn Met Leu Ser Arg Phe Cys Leu
1 5 10 15
Phe Leu Ile Met Leu Leu His Ile Leu Leu Phe Leu Val Ile Phe Ile
20 25 30
Gln Arg His Thr Val Val Ser Leu Ser Lys His His Pro Phe Val Pro
35 40 45
Thr Asn Gly Ser Lys Ser Tyr Ser Ser Phe Xaa
50 55

<210> 163
<211> 374
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (84)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE

<222> (112)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 163

```

Met Arg Pro Gly Thr Ala Leu Gln Ala Val Leu Leu Ala Val Leu Leu
 1           5           10           15

Val Gly Leu Arg Ala Ala Thr Gly Arg Leu Leu Ser Gly Gln Pro Val
          20           25           30

Cys Arg Gly Gly Thr Gln Arg Pro Cys Tyr Lys Val Ile Tyr Phe His
          35           40           45

Asp Thr Ser Arg Arg Leu Asn Phe Glu Glu Ala Lys Glu Ala Cys Arg
          50           55           60

Arg Asp Gly Gly Gln Leu Val Ser Ile Glu Ser Glu Asp Glu Gln Lys
          65           70           75           80

Leu Ile Glu Xaa Phe Ile Glu Asn Leu Leu Pro Ser Asp Gly Asp Phe
          85           90           95

Trp Ile Gly Leu Arg Arg Arg Glu Glu Lys Gln Ser Asn Ser Thr Xaa
          100          105          110

Cys Gln Asp Leu Tyr Ala Trp Thr Asp Gly Ser Ile Ser Gln Phe Arg
          115          120          125

Asn Trp Tyr Val Asp Glu Pro Ser Cys Gly Ser Glu Val Cys Val Val
          130          135          140

Met Tyr His Gln Pro Ser Ala Pro Ala Gly Ile Gly Gly Pro Tyr Met
          145          150          155          160

Phe Gln Trp Asn Asp Asp Arg Cys Asn Met Lys Asn Asn Phe Ile Cys
          165          170          175

Lys Tyr Ser Asp Glu Lys Pro Ala Val Pro Ser Arg Glu Ala Glu Gly
          180          185          190

Glu Glu Thr Glu Leu Thr Thr Pro Val Leu Pro Glu Glu Thr Gln Glu
          195          200          205

Glu Asp Ala Lys Lys Thr Phe Lys Glu Ser Arg Glu Ala Ala Leu Asn
          210          215          220

Leu Ala Tyr Ile Leu Ile Pro Ser Ile Pro Leu Leu Leu Leu Val
          225          230          235          240

Val Thr Thr Val Val Cys Trp Val Trp Ile Cys Arg Lys Arg Lys Arg
          245          250          255

Glu Gln Pro Asp Pro Ser Thr Lys Lys Gln His Thr Ile Trp Pro Ser
          260          265          270

Pro His Gln Gly Asn Ser Pro Asp Leu Glu Val Tyr Asn Val Ile Arg
          275          280          285

Lys Gln Ser Glu Ala Asp Leu Ala Glu Thr Arg Pro Asp Leu Lys Asn

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116

290 295 300
 Ile Ser Phe Arg Val Cys Ser Gly Glu Ala Thr Pro Asp Asp Met Ser
 305 310 315 320
 Cys Asp Tyr Asp Asn Met Ala Val Asn Pro Ser Glu Ser Gly Phe Val
 325 330 335
 Thr Leu Val Ser Val Glu Ser Gly Phe Val Thr Asn Asp Ile Tyr Glu
 340 345 350
 Phe Ser Pro Asp Gln Met Gly Arg Ser Lys Glu Ser Gly Trp Val Glu
 355 360 365
 Asn Glu Ile Tyr Gly Tyr
 370

<210> 164
 <211> 64
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (64)
 <223> Xaa equals stop translation

<400> 164
 Met His Pro Gln Leu Ile Pro Ser Val Ile Ala Val Val Phe Ile Leu
 1 5 10 15
 Leu Leu Gly Val Cys Phe Ile Ala Ser Cys Leu Val Thr His His Asn
 20 25 30
 Phe Ser Arg Cys Lys Arg Gly Thr Gly Val His Lys Leu Glu His His
 35 40 45
 Ala Lys Leu Lys Cys Ile Lys Glu Lys Ser Glu Leu Lys Ser Cys Xaa
 50 55 60

<210> 165
 <211> 743
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (743)
 <223> Xaa equals stop translation

<400> 165
 Met Ala Val Arg Glu Leu Cys Phe Pro Arg Gln Arg Gln Val Leu Phe
 1 5 10 15

Leu Phe Leu Phe Trp Gly Val Ser Leu Ala Gly Ser Gly Phe Gly Arg
 20 25 30
 Tyr Ser Val Thr Glu Glu Thr Glu Lys Gly Ser Phe Val Val Asn Leu
 35 40 45
 Ala Lys Asp Leu Gly Leu Ala Glu Gly Glu Leu Ala Ala Arg Gly Thr
 50 55 60
 Arg Val Val Ser Asp Asp Asn Lys Gln Tyr Leu Leu Leu Asp Ser His
 65 70 75 80
 Thr Gly Asn Leu Leu Thr Asn Glu Lys Leu Asp Arg Glu Lys Leu Cys
 85 90 95
 Gly Pro Lys Glu Pro Cys Met Leu Tyr Phe Gln Ile Leu Met Asp Asp
 100 105 110
 Pro Phe Gln Ile Tyr Arg Ala Glu Leu Arg Val Arg Asp Ile Asn Asp
 115 120 125
 His Ala Pro Val Phe Gln Asp Lys Glu Thr Val Leu Lys Ile Ser Glu
 130 135 140
 Asn Thr Ala Glu Gly Thr Ala Phe Arg Leu Glu Arg Ala Gln Asp Pro
 145 150 155 160
 Asp Gly Gly Leu Asn Gly Ile Gln Asn Tyr Thr Ile Ser Pro Asn Ser
 165 170 175
 Phe Phe His Ile Asn Ile Ser Gly Gly Asp Glu Gly Met Ile Tyr Pro
 180 185 190
 Glu Leu Val Leu Asp Lys Ala Leu Asp Arg Glu Glu Gln Gly Glu Leu
 195 200 205
 Ser Leu Thr Leu Thr Ala Leu Asp Gly Gly Ser Pro Ser Arg Ser Gly
 210 215 220
 Thr Ser Thr Val Arg Ile Val Val Leu Asp Val Asn Asp Asn Ala Pro
 225 230 235 240
 Gln Phe Ala Gln Ala Leu Tyr Glu Thr Gln Ala Pro Glu Asn Ser Pro
 245 250 255
 Ile Gly Phe Leu Ile Val Lys Val Trp Ala Glu Asp Val Asp Ser Gly
 260 265 270
 Val Asn Ala Glu Val Ser Tyr Ser Phe Phe Asp Ala Ser Glu Asn Ile
 275 280 285
 Arg Thr Thr Phe Gln Ile Asn Pro Phe Ser Gly Glu Ile Phe Leu Arg
 290 295 300
 Glu Leu Leu Asp Tyr Glu Leu Val Asn Ser Tyr Lys Ile Asn Ile Gln
 305 310 315 320
 Ala Met Asp Gly Gly Gly Leu Ser Ala Arg Cys Arg Val Leu Val Glu
 325 330 335

Val Leu Asp Thr Asn Asp Asn Pro Pro Glu Leu Ile Val Ser Ser Phe
 340 345 350
 Ser Asn Ser Val Ala Glu Asn Ser Pro Glu Thr Pro Leu Ala Val Phe
 355 360 365
 Lys Ile Asn Asp Arg Asp Ser Gly Glu Asn Gly Lys Met Val Cys Tyr
 370 375 380
 Ile Gln Glu Asn Leu Pro Phe Leu Leu Lys Pro Ser Val Glu Asn Phe
 385 390 395 400
 Tyr Ile Leu Ile Thr Glu Gly Ala Leu Asp Arg Glu Ile Arg Ala Glu
 405 410 415
 Tyr Asn Ile Thr Ile Thr Val Thr Asp Leu Gly Thr Pro Arg Leu Lys
 420 425 430
 Thr Glu His Asn Ile Thr Val Leu Val Ser Asp Val Asn Asn Asn Ala
 435 440 445
 Pro Ala Phe Thr Gln Thr Ser Tyr Thr Leu Phe Val Arg Glu Asn Asn
 450 455 460
 Ser Pro Ala Leu His Ile Gly Ser Val Ser Ala Thr Asp Arg Asp Ser
 465 470 475 480
 Gly Thr Asn Ala Gln Val Thr Tyr Ser Leu Leu Pro Pro Gln Asp Pro
 485 490 495
 His Leu Pro Leu Ala Ser Leu Val Ser Ile Asn Ala Asp Asn Gly His
 500 505 510
 Leu Phe Ala Leu Arg Ser Leu Asp Tyr Glu Ala Leu Gln Ala Phe Glu
 515 520 525
 Phe Arg Val Gly Ala Thr Asp Arg Gly Ser Pro Ala Leu Asn Ser Glu
 530 535 540
 Ala Leu Gly Ala Arg Ala Gly Ala Gly Arg Gln Arg Gln Leu Ala Leu
 545 550 555 560
 Arg Ala Val Pro Ala Ala Glu Arg Leu Arg Ala Leu His Arg Ala Gly
 565 570 575
 Ala Pro Gly Gly Arg Ala Gly Leu Pro Gly Asp Gln Gly Gly Gly Gly
 580 585 590
 Gly Arg Arg Leu Gly Pro Glu Arg Leu Ala Val Val Pro Ala Ala Gln
 595 600 605
 Gly His Gly Ala Arg Ala Val Arg Cys Val Gly Ala Gln Trp Gly Gly
 610 615 620
 Ala His Arg Gln Ala Ala Glu Arg Ala Arg Arg Ser Gln Ala Gln Ala
 625 630 635 640
 Gly Gly Ala Cys Gln Gly Gln Trp Arg Ala Ser Ser Leu Gly His Arg

Gly Gly Arg Glu Gly Arg Xaa
740

<223> Xaa equals stop translation

Ser Arg Ile His Arg Glu Glu Asp Phe Gln Phe Ile Leu Lys Gly Ile
130 135 140

Ala Arg Leu Leu Ser Asn Pro Leu Leu Gln Thr Tyr Leu Pro Asn Ser
145 150 155 160

Thr Lys Lys Asp Pro Val Pro Pro Gly Ala Ala Ser Ser Leu Leu Glu
165 170 175

Ala Leu Arg Leu Gln Gln Glu Ile Pro Leu Leu Arg Ala Glu Glu Gln
180 185 190

Arg Arg Pro Arg His Pro Cys Pro His Pro Leu Leu Pro Gln Arg Cys
195 200 205

Pro Gly Arg Ser Val Xaa
210

<210> 167

<211> 213

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (213)

<223> Xaa equals stop translation

<400> 167

Met Pro Ser Leu Arg Phe Leu Ala Leu Ala Leu Leu Ala Ile Leu
1 5 10 15

Pro Ala Leu Pro Asn Ala His Ala Ala Pro Gly Ile Gly Gly Leu Ile
20 25 30

Gly Gly Gly Ser Gln Ala Ser Ala Lys Glu Glu Pro Gln Ser Asn Ala
35 40 45

Gln Pro Ser Ala Asp Glu Arg Lys Gln Arg Leu Leu Ser Gln Ala Glu
50 55 60

Glu Thr Arg Gln Arg Leu Thr Asp Leu Lys Ala Glu Leu Ala Gly Ala
65 70 75 80

Pro Lys Glu Ile Ser Glu Ala Gln Arg Thr Leu Ser Lys Leu Val Ser
85 90 95

Glu Asp Asn Ser Asp Leu Pro Glu Arg Leu Ser Lys Leu Ser Val Pro
100 105 110

Val Leu Glu Gln Arg Leu Ala Ala Arg Val Asp Glu Leu Ala Leu Trp
115 120 125

Gln Gln Ala Leu Ser Ala Ala Asn Ser Met Leu Ile Ser Ala Gln Thr
130 135 140

Arg Pro Glu Arg Ala Gln Ala Asp Ile Ser Lys Asn Gln Leu Arg Ile
145 150 155 160

Asp Glu Ile Asn Gly Leu Leu Lys Ser Gly Arg Glu Asn Asn Lys Pro
165 170 175

Leu Thr Asp Glu Arg Arg Ala Leu Leu Glu Ser Thr Ser Arg Ala Ala
 180 185 190

Ala Gly Pro Ser Ile Phe His Pro Gly Gly Val Pro Gly Lys Cys Thr
 195 200 205

Gln Phe Ala Leu Xaa
 210

<210> 168

<211> 75

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (75)

<223> Xaa equals stop translation

<400> 168

Met Phe Thr Ser Phe Gly Leu Ala Ser Pro Arg Ile Leu Phe Cys Phe
 1 5 10 15

Cys Phe Phe Asp Leu Gly Phe Ile Phe Phe Cys Val Leu Tyr Tyr Ile
 20 25 30

Val Lys Gly Ile Leu Ala Glu Thr Leu Val Phe Gly Ala Arg Gly Glu
 35 40 45

Gln Glu Cys Trp Ala Val Tyr Phe Arg Trp Arg Thr His Leu Gln Thr
 50 55 60

Phe Gly Leu Phe Ser Phe Asn Cys Ser Val Xaa
 65 70 75

<210> 169

<211> 48

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (48)

<223> Xaa equals stop translation

<400> 169

Met Phe Leu Cys Leu Phe Phe Phe Phe Phe Asn Ala Thr Gln Gly Asn
 1 5 10 15

Ile Phe Ile Ser Phe Leu Ser Gly Leu Pro Gln Cys Ile Phe Ile Ser
 20 25 30

Phe Glu Thr Lys Arg Phe Trp Lys Leu Phe Phe Cys Ser Phe Lys Xaa
 35 40 45

<210> 170
 <211> 88
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (88)
 <223> Xaa equals stop translation

<400> 170
 Met Gly Leu His Leu Arg Pro Tyr Arg Val Gly Leu Leu Pro Asp Gly
 1 5 10 15
 Leu Leu Phe Leu Leu Leu Leu Met Leu Leu Ala Asp Pro Ala Leu
 20 25 30
 Pro Ala Gly Arg His Pro Pro Val Val Leu Val Pro Gly Asp Leu Gly
 35 40 45
 Asn Gln Leu Glu Ala Lys Leu Asp Lys Pro Thr Val Val His Tyr Leu
 50 55 60
 Cys Ser Lys Lys Thr Glu Ser Tyr Phe Thr Ile Trp Leu Asn Leu Glu
 65 70 75 80
 Leu Leu Leu Pro Val His His Xaa
 85

<210> 171
 <211> 42
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (42)
 <223> Xaa equals stop translation

<400> 171
 Met Ala Cys Glu Thr His Gly Val Leu Val Pro Ala His Leu Ser Gly
 1 5 10 15
 Leu Ile Thr Cys Leu Leu Ala Phe Trp Val Pro Ala Ser Cys Ile Gln
 20 25 30
 Arg Cys Ser Gly Ser Pro Leu Pro Leu Xaa
 35 40

<210> 172
 <211> 48
 <212> PRT
 <213> Homo sapiens

123

<220>

<221> SITE

<222> (48)

<223> Xaa equals stop translation

<400> 172

Met Gln Cys Phe Leu Phe Ser Ile Phe Leu Ile Thr Gly Leu Ala Glu
 1 5 10 15

Glu Phe Cys Glu Gln Leu Ser Ile Ser Leu Ala Glu Glu Glu Ile Gln
 20 25 30

Leu Ser Ser Thr Val Glu His Phe Cys Met Thr Ala Phe Ser Trp Xaa
 35 40 45

<210> 173

<211> 233

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (233)

<223> Xaa equals stop translation

<400> 173

Met Ala Ala Leu Ala Ala Ala Lys Lys Val Trp Ser Ala Arg Arg
 1 5 10 15

Leu Leu Val Leu Leu Phe Thr Pro Leu Ala Leu Leu Pro Val Val Phe
 20 25 30

Ala Leu Pro Pro Lys Glu Gly Arg Cys Leu Phe Val Ile Leu Leu Met
 35 40 45

Ala Val Tyr Trp Cys Thr Glu Ala Leu Pro Leu Ser Val Thr Ala Leu
 50 55 60

Leu Pro Ile Val Leu Phe Pro Phe Met Gly Ile Leu Pro Ser Asn Lys
 65 70 75 80

Val Cys Pro Gln Tyr Phe Leu Asp Thr Asn Phe Leu Phe Leu Ser Gly
 85 90 95

Leu Ile Met Ala Ser Ala Ile Glu Glu Trp Asn Leu His Arg Arg Ile
 100 105 110

Ala Leu Lys Ile Leu Met Leu Val Gly Val Gln Pro Ala Arg Leu Ile
 115 120 125

Leu Gly Met Met Val Thr Thr Ser Phe Leu Ser Met Trp Leu Ser Asn
 130 135 140

Thr Ala Ser Thr Ala Met Met Leu Pro Ile Ala Asn Ala Ile Leu Lys
 145 150 155 160

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<210> 174
<211> 45
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (45)
<223> Xaa equals stop translation
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<400> 174
Met Gly Thr Ile Phe Gly Tyr Leu His Cys Val Lys Cys Tyr Val Leu
  1             5             10             15
Tyr Phe Ile Phe Ile Leu Ile Thr Ala Val Tyr His Ser Phe Tyr Tyr
      20             25             30
Pro His Tyr Arg Gly Lys Ala Leu Ile Ser Gly Thr Xaa
      35             40             45

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<210> 175
<211> 85
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (77)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (85)
<223> Xaa equals stop translation
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<400> 175
Met Val Trp Phe Leu Phe Leu Val Phe Ile Phe Leu Lys Val Lys Gly
  1             5             10             15
Asp Phe Phe Pro Pro Phe Leu Ile Cys Asn Leu Phe Cys Ile Trp Met
      20             25             30

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Ile Thr Gly Val Ser His Arg Leu Gln Pro Gln Ile Leu Phe Ser Arg
 35 40 45
 His Lys His Asn Gln Glu Ile Ile Leu Gln Met Val Ser Phe Ser Cys
 50 55 60
 Cys Val Phe Phe Pro Met Ile Arg Glu Val Lys Ser Xaa Leu Gly Cys
 65 70 75 80
 Ile Lys Met Ser Xaa
 85

<210> 176
 <211> 66
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SITE
 <222> (66)
 <223> Xaa equals stop translation

<400> 176
 Met Trp Val Leu Leu Ser Cys Pro Leu Pro Pro Leu Cys Leu Pro Ala
 1 5 10 15
 Ser Ala Val Pro Gly Gln Cys Leu Gly Gly Gln Trp Ser Gly His Gln
 20 25 30
 Leu Arg Leu Arg Gly Arg Gly Trp His Cys Arg Cys His Cys Arg Ala
 35 40 45
 Trp Ala Ala Asp Met Gly Arg Gly Leu His Ser Cys Gln Leu Leu Ser
 50 55 60
 Arg Xaa
 65

<210> 177
 <211> 55
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (55)
 <223> Xaa equals stop translation

<400> 177
 Met Leu Leu Leu Cys Ile Leu Leu Ile Phe Cys Val Val Gly Leu Ser
 1 5 10 15
 Val Val Gly Arg Arg Val Leu Lys Ser Thr Thr Ile Ile Val Tyr Leu
 20 25 30
 Ser Ile Thr Pro Phe Ser Ser Phe Ser Ser Ile Ser His Ile Phe Gln

35 40 45
 Leu Leu Ile Gly Ala His Xaa
 50 55

 <210> 178
 <211> 83
 <212> PRT
 <213> Homo sapiens

 <220>
 <221> SITE
 <222> (4)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (83)
 <223> Xaa equals stop translation

 <400> 178
 Met Cys Val Xaa Leu Ser Phe Cys Pro Phe Leu Ser Ser Ala Leu Pro
 1 5 10 15
 Ala Ser His Thr Gln Phe Tyr Met Pro Arg Gly Ala Lys Phe Gly Thr
 20 25 30
 Phe Thr Leu Gln Ala Ser Val Ser Pro Leu Glu Glu Lys Thr His Ser
 35 40 45
 Phe Thr His Pro Gly Ile Gly Gly Lys Leu Leu Gly His Gln Asp Pro
 50 55 60
 Gly Ala Pro Gly Pro Ser Trp Asn Ile Arg Ser Thr Trp Ser Thr Arg
 65 70 75 80
 Ser Leu Xaa

<210> 179
 <211> 330
 <212> PRT
 <213> Homo sapiens

 <220>
 <221> SITE
 <222> (38)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (247)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <400> 179
 Met Ser Pro Leu Ser Ala Ala Arg Ala Ala Leu Arg Val Tyr Ala Val
 1 5 10 15

Gly Ala Ala Val Ile Leu Ala Gln Leu Leu Arg Arg Cys Arg Gly Gly
 20 25 30
 Phe Leu Glu Pro Val Xaa Pro Pro Arg Pro Asp Arg Val Ala Ile Val
 35 40 45
 Thr Gly Gly Thr Asp Gly Ile Gly Tyr Ser Thr Ala Lys His Leu Ala
 50 55 60
 Arg Leu Gly Met His Val Ile Ile Ala Gly Asn Asn Asp Ser Lys Ala
 65 70 75 80
 Lys Gln Val Val Ser Lys Ile Lys Glu Glu Thr Leu Asn Asp Lys Val
 85 90 95
 Glu Phe Leu Tyr Cys Asp Leu Ala Ser Met Thr Ser Ile Arg Gln Phe
 100 105 110
 Val Gln Lys Phe Lys Met Lys Lys Ile Pro Leu His Val Leu Ile Asn
 115 120 125
 Asn Ala Gly Val Met Met Val Pro Gln Arg Lys Thr Arg Asp Gly Phe
 130 135 140
 Glu Glu His Phe Gly Leu Asn Tyr Leu Gly His Phe Leu Leu Thr Asn
 145 150 155 160
 Leu Leu Leu Asp Thr Leu Lys Glu Ser Gly Ser Pro Gly His Ser Ala
 165 170 175
 Arg Val Val Thr Val Ser Ser Ala Thr His Tyr Val Ala Glu Leu Asn
 180 185 190
 Met Asp Asp Leu Gln Ser Ser Ala Cys Tyr Ser Pro His Ala Ala Tyr
 195 200 205
 Ala Gln Ser Lys Leu Ala Leu Val Leu Phe Thr Tyr His Leu Gln Arg
 210 215 220
 Leu Leu Ala Ala Glu Gly Ser His Val Thr Ala Asn Val Val Asp Pro
 225 230 235 240
 Gly Val Val Asn Thr Asp Xaa Tyr Lys His Val Phe Trp Ala Thr Arg
 245 250 255
 Leu Ala Lys Lys Leu Leu Gly Trp Leu Leu Phe Lys Thr Pro Asp Glu
 260 265 270
 Gly Ala Trp Thr Ser Ile Tyr Ala Ala Val Thr Pro Glu Leu Glu Gly
 275 280 285
 Val Gly Gly Arg Tyr Leu Tyr Asn Glu Lys Glu Thr Lys Ser Leu His
 290 295 300
 Val Thr Tyr Asn Gln Lys Leu Gln Gln Gln Leu Trp Ser Lys Ser Cys
 305 310 315 320
 Glu Met Thr Gly Val Leu Asp Val Thr Leu

325

330

<210> 180
<211> 41
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (41)
<223> Xaa equals stop translation

<400> 180
Met Ile Ala Cys Gln Tyr Ile Ser Leu Ala Ile Met Leu Ala Phe Val
1 5 10 15
Arg Trp Ala Ala Phe Leu Leu Phe Pro Phe Leu Cys Gly Asp Asn Gly
20 25 30
Gly Asn Ile Gln Gln Lys Tyr Val Xaa
35 40

<210> 181
<211> 52
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (52)
<223> Xaa equals stop translation

<400> 181
Met Ala Asn Ala Met Ala Tyr Leu Ser Ile Phe Leu Cys Gly Ala Ser
1 5 10 15
Ser Ser Pro Cys Asp Cys Ala Leu Leu Val Pro Val Ser Leu Phe Arg
20 25 30
Gly Arg Lys Val Ala Asn Phe Lys Asn Gln Asn Ser Asp Val Thr Ser
35 40 45
Gly Asn Ala Xaa
50

<210> 182
<211> 55
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (55)
<223> Xaa equals stop translation

<400> 182

129

Met Gln Gln Ile Cys Ser Cys Leu Gly Ala Phe Ala Leu Leu Phe Phe
 1 5 10 15
 Trp Pro Gly His Phe Thr Ser Thr Phe Ser Ile Phe Tyr Asp Phe Leu
 20 25 30
 Pro Ile Phe Gly Ser Leu Phe Lys Cys His Pro Ser Lys Arg Pro Ser
 35 40 45
 Lys Leu Pro Tyr Leu Lys Xaa
 50 55

<210> 183
 <211> 62
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SITE
 <222> (62)
 <223> Xaa equals stop translation

<400> 183
 Met Arg Leu Leu Leu Glu Trp Arg Val Tyr Leu Arg Leu Thr Cys Ala
 1 5 10 15
 Thr Lys Asp Gly Met Ala Arg Glu Cys Pro Thr Thr Trp Leu Ser Pro
 20 25 30
 Pro Ala Lys Pro Asp Phe Ala Gln Arg His Ser Val Lys Pro Thr Ala
 35 40 45
 Leu Gln Gly Gly Arg Trp Ser Arg Leu Gly Ala Ser Pro Xaa
 50 55 60

<210> 184
 <211> 148
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SITE
 <222> (148)
 <223> Xaa equals stop translation

<400> 184
 Met Leu Gly Leu Pro Trp Lys Gly Gly Leu Ser Trp Ala Leu Leu Leu
 1 5 10 15
 Leu Leu Leu Gly Ser Gln Ile Leu Leu Ile Tyr Ala Trp His Phe His
 20 25 30
 Glu Gln Arg Asp Cys Asp Glu His Asn Val Met Ala Arg Tyr Leu Pro
 35 40 45
 Ala Thr Val Glu Phe Ala Val His Thr Phe Asn Gln Gln Ser Lys Asp
 50 55 60